# SYNOPSIS OF
# VETERINARY PHARMACOLOGY AND TOXICOLOGY

5 hydroxy tryptamine (serotonin)

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# CONTENTS


| | | | |
|---|---|---|---|
| | | **SECTION I: GENERAL PHARMACOLOGY** | |
| Chapter 1 | | **INTRODUCTION** | |
| | 1. | Historical Background | 1 |
| | 2. | Definitions and Branches of Pharmacology | 2 |
| | 3. | Drug Development, Screening and Nomeclature | 3 |
| | 4. | Scope of Veterinary Pharmacology | 6 |
| | EXERCISE | | 6 |
| Chapter 2 | | **SOURCES, CLASSIFICATION AND ADMINISTRATION OF DRUGS** | |
| | 1. | Soucres of Drugs | 8 |
| | 2. | Active Principles of Medicinal Plants | 9 |
| | 3. | Pharmacotherapeutic Classification of Drugs | 12 |
| | 4. | Administration of Drugs | 14 |
| | EXERCISE | | 18 |
| Chapter 3 | | **PRINCIPLES OF DRUG ACTION: PHARMACOKINETICS** | |
| | 1. | Drug Absorption | 19 |
| | 2. | Distribution of Drugs | 20 |
| | 3. | Metabolism of Drugs | 21 |
| | 4. | Drug Excretion | 24 |
| | EXERCISE | | 25 |
| Chapter 4 | | **PRINCIPLES OF DRUG ACTION: PHARMACODYNAMICS** | |
| | 1. | Mechanism of Drug Action | 28 |
| | 2. | Pharmacometrics | 33 |
| | 3. | Drug Potency | 33 |
| | 4. | Drug Assay | 34 |
| | 5. | Combined Action of Drugs | 35 |
| | 6. | Structure of Activity Relationship | 36 |
| | EXERCISE | | 37 |
| Chapter 5 | | **FACTORS MODIFYING DRUG RESPONSES** | 40 |
| | EXEXRCISE | | 43 |
| Chapter 6 | | **ADEVERSE DRUG REACTIONS AND DRUG TOXICITY** | 45 |
| | EXERCISE | | 46 |
| | | **SECTION II: ANS AND AUTACOID PHARMACOLOGY** | |
| Chapter 7 | | **PHYSIOLOGICAL (GENERAL) CONSIDERATIONS** | |
| | 1. | Impulse Conduction | 47 |
| | 2. | Impulse Transmission | 47 |
| Chapter 8 | | **CHOLINERGIC TRANSMISSION** | 49 |
| Chapter 9 | | **NONADRENERGIC (ADRENERGIC) TRANSMISSION** | 51 |
| Chapter 10 | | **PHARMACOLOGY OF CHOLINERGIC SYSTEM** | |
| | 1. | Parasympathomimetics | 54 |
| | 2. | Parasympatholytics | 56 |
| | 3. | Ganglionic Stimulants | 58 |
| | 4. | Ganglionic Blockers | 58 |
| | 5. | Neuromuscular Transmission | 59 |
| Chapter 11 | | **PHARMACOLOGY OF NORADRENERGIC TRANSMISSION** | |
| | 1. | Sympathomimetics | 60 |
| | 2. | Sympatholytics | 62 |
| | EXERCISE (All ANS) | | 64 |
| Chapter 12 | | **AUTACOIDS** | |
| | 1. | Histamine | 69 |
| | 2. | Antihistamines | 71 |
| | 3. | 5-Hydroxytryptamine | 73 |
| | 4. | Kinins: Kallidin and Bradykinin | 74 |
| | 5. | Angiotensins | 74 |
| | 6. | Eicosanoids | 75 |
| | 7. | Platelet Activating Factor | 78 |
| | EXERCISE | | 79 |

| | | | |
|---|---|---|---|
| | | **SECTION III: CNS PHARMACOLOGY** | |
| Chapter 13 | | **TRANSMITTERS IN CNS** | 86 |
| Chapter 14 | | **GENERAL ANAESTHETICS – INTRODUCTION** | |
| | 1. | Historical Background | 87 |
| | 2. | Definitions | 87 |
| | 3. | Theories of General Anaesthesia | 88 |
| | 4. | Stages of Anaesthesia | 88 |
| Chapter 15 | | **INHALATION ANAESTHETICS** | |
| | 1. | Major Volatile Anaesthetics | 90 |
| | 2. | Other Volatile Anaesthetics | 91 |
| | 3. | Anaesthetic Gases | 92 |
| Chapter 16 | | **INTRAVENOUS ANAESTHETICS** | |
| | 1. | Barbiturates | 93 |
| | 2. | Chloral Hydrate | 95 |
| | 3. | Dissociative Anaesthetics | 95 |
| | 4. | Other Parenteral Anaesthetics | 96 |
| | 5. | Preanaeshetic Medication | 96 |
| Chapter 17 | | **SEDATIVES, HYPNOTICS AND ANTICONVULSANTS** | 98 |
| Chapter 18 | | **TRANQUILIZERS AND ANTIPSYCHOTICS** | 100 |
| Chapter 19 | | **ANALGESICS** | |
| | 1. | Introduction | 103 |
| | 2. | Narcotic Analgesics | 103 |
| | 3. | Nanonarcotic Analgesics: NASAIDs | 106 |
| | 4. | Other Analgesics | 108 |
| Chapter 20 | | **CNS STIMULANTS** | 109 |
| | EXERCISE (All CNS) | | 110 |
| Chapter 21 | | **PHARMACOLOGY OF SOMATIC NERVES** | |
| | 1. | Local Anaesthetics | 114 |
| | 2. | Skeletal Muscle Relaxants | 115 |
| | EXERCISE | | 116 |
| | | **SECTION IV: SYSTEMIC PHARMACOLOGY** | |
| Chapter 22 | | **DRUGS ACTING ON DIGESTIVE SYSTEM** | |
| | 1. | Sialagogues and Atisialagogues | 118 |
| | 2. | Stomachics and Antistomachics | 118 |
| | 3. | Carminatives | 118 |
| | 4. | Emetics and Antiemetics | 118 |
| | 5. | Cholagogues and Choleritics | 119 |
| | 6. | Intestinal Astringents | 120 |
| | 7. | Appetizers | 120 |
| | 8. | Anorexigenics | 120 |
| | 9. | Antacids | 120 |
| | 10. | Antiulcer Drugs | 121 |
| | 11. | Prokinetics | 121 |
| | 12. | Antizymotics | 122 |
| | 13. | Antidiarrhoeals | 122 |
| | 14. | Purgatives | 122 |
| | 15. | Pharmacological Considerations of Rumen | 125 |
| | 16. | Rumino-reticular Pharmacotherapeutics | 125 |
| | EXERCISE | | 126 |
| Chapter 23 | | **DRUGS ACTING ON CARDIOVACULAR SYSTEM** | |
| | 1. | Cardiotonics | 129 |
| | 2. | Cardiac Stimulants | 131 |
| | 3. | Antiarrhythmic Drugs | 132 |
| | 4. | Antihypertensive Drugs | 133 |
| | 5. | Haematinics | 134 |
| | 6. | Blood Cogulants | 134 |
| | 7. | Blood Anticogulants | 135 |
| | EXERCISE | | 136 |

| | | | |
|---|---|---|---|
| Chapter 24 | | **DRUGS ACTING ON RESPIRATORY SYSTEM** | |
| | 1. | Antitussives | 140 |
| | 2. | Expectorants | 140 |
| | 3. | Bronchodilators | 141 |
| | 4. | Analeptics | 141 |
| | EXERCISE | | 142 |
| Chapter 25 | | **DRUGS ACTING ON URINARY SYSTEM AND FLUID THERAPY** | |
| | 1. | Diuretics | 143 |
| | 2. | Urinary Alkalizers | 145 |
| | 3. | Urinary Acidifiers | 145 |
| | 4. | Urinary Antiseptics | 145 |
| | 5. | Fluid and Electrolyte Therapy | 146 |
| | EXERCISE | | 146 |
| Chapter 26 | | **DRUGS ACTING ON UTERUS** | |
| | 1. | Oxytocics | 148 |
| | 2. | Tocolytics and Relaxin | 149 |
| | Exercise | | 149 |
| Chapter 27 | | **DRUGS ACTING ON MUCOUS MEMBRANES AND SKIN** | |
| | 1. | Emollients | 151 |
| | 2. | Demulcents | 151 |
| | 3. | Astringents | 151 |
| | 4. | Adsorbents and Protectants | 151 |
| | 5. | Antipruritics | 151 |
| | 6. | GI Mucosal Protectants | 151 |
| | 7. | Keratolytics | 151 |
| | 8. | Caustics and Escharotics | 152 |
| | 9. | Counter Irritants | 152 |
| | 10. | Wound Healers | 152 |
| | EXERCISE | | 152 |
| Chapter 28 | | **VITAMIN PHARMACOLOGY** | |
| | 1. | Therapy of Fat Soluble Vitamin Deficiency | 154 |
| | 2. | Therapy of Water Soluble Vitamin Deficiency | 154 |
| | EXERCISE | | 155 |
| Chapter 29 | | **ENDOCRINE PHARMACOLOGY** | |
| | 1. | Hypothalamic Hormones and Agonists/Antagonists | 156 |
| | 2. | Anterior Pituitary Hormones and Agonists/Antagonists | 156 |
| | 3. | Posterior Pituitary and Hormones Agonists/Antagonists | 157 |
| | 4. | Adrenal Corticosteroids | 157 |
| | 5. | Thyroid Hormones and Antithyroid Drugs | 158 |
| | 6. | Paratharmone and Calcitonin | 159 |
| | 7. | Insulin and Oral Hypoglycaemic Drugs | 160 |
| | 8. | Glucagon | 161 |
| | 9. | Somatostatin | 161 |
| | 10. | Amylin | 161 |
| | 11. | Female Sex Hormones: Agonists and Antagonists | 161 |
| | 12. | Male Sex Hormones: Agonists and Antagonists | 162 |
| | 13. | Reproduction Therapy in Animals | 163 |
| | EXERCISE | | 164 |
| Chapter 30 | | **PRODUCTION PHARMACOLOGY** | |
| | 1. | Growth Promoters | 166 |
| | 2. | Anabolic Steroids | 167 |
| | 3. | Therapy of Milk Fever | 167 |
| | 4. | Therapy of Ketosis | 167 |
| | 5. | Therapy of Post-Parturient Haemoglobinuria | 167 |
| | EXERCISE | | 168 |
| Chapter 31 | | **IMMUNOPHARMACOLOGY AND BIOENHANCERS** | |
| | 1. | Immunosuppressants | 169 |
| | 2. | Immunostimulants | 170 |
| | 3. | Bioenhancers | 171 |
| | EXERCISE | | 172 |

## SECTION V: CHEMOTHERAPY


| | | | |
|---|---|---|---|
| Chapter 32 | | **GENERAL CONSIDERATIONS** | |
| | 1. | Historical Background | 174 |
| | 2. | Classification of Antimicrobial Agents | 175 |
| | 3. | Principles of Chemotherapy | 176 |
| | 4. | Selection of Antimicrobial Agent | 176 |
| | 5. | Cmplications of Antimicrobial Therapy | 179 |
| | 6. | Microbial Resistance | 180 |
| | 7. | Combination of Antimicrobial Agents | 181 |
| | 8. | Misuses of Antimicrobial Agents | 182 |
| | EXERCISE | | 182 |
| Chapter 33 | | **ANTIBACTERIAL AGENTS** | |
| | 1. | Sulfonamides | 185 |
| | 2. | Potentiated Sulfonamides | 188 |
| | 3. | Nitrofurans | 189 |
| | 4. | Sulfones | 189 |
| | EXERCISE | | 189 |
| Chapter 34 | | **ANTIBIOTICS** | |
| | 1. | Beta-Lactam Antibiotics | 191 |
| | 2. | Aminoglycoside Antibiotics | 196 |
| | 3. | Tetracyclines | 198 |
| | 4. | Chloramphenicol and Congeners | 201 |
| | 5. | Macrolide Antibiotics | 202 |
| | 6. | Lincosamides | 204 |
| | 7. | Quinolones and Fluoroquinolones | 205 |
| | 8. | Antitubercular Drugs | 206 |
| | 9. | Miscellaneous Antibacterial Agets | 207 |
| | EXERCISE | | 209 |
| Chapter 35 | | **ANTIFUNGAL AGENTS** | 214 |
| | EXERCISE | | 217 |
| Chapter 36 | | **ANTIVIRAL DRUGS** | 219 |
| | EXERCISE | | 222 |
| Chapter 37 | | **ANTISEPTICS AND DISINFECTANTS** | 224 |
| | EXERCISE | | 228 |
| Chapter 38 | | **ANTINEOPLASTIC DRUGS** | 229 |
| | EXERCISE | | 233 |
| Chapter 39 | | **TREATMENT OF WORM INFESTATION** | |
| | **1.** | **Anthelmintics** | |
| | a. | Classification | 235 |
| | b. | Ideal Anthelmintic | 236 |
| | c. | General Mode of Action | 237 |
| | d. | Anthelmintic Resistance | 238 |
| | **2.** | **Antinematodal Drugs** | |
| | a. | Simple Heterocyclic Compounds | 239 |
| | b. | Benzimidazoles | 241 |
| | c. | Imidazothiazoles | 243 |
| | d. | Tetrahydropyrimidines | 244 |
| | e. | Organophosphorus Compounds | 244 |
| | f. | Macrocyclic Lactones | 245 |
| | g. | Drugs Against Heartworm | 246 |
| | h. | Miscellaneous Antinematodal Drugs | 248 |
| | **3.** | **Anticestodal Drugs** | |
| | a. | Natural Compounds | 249 |
| | b. | Synthetic Organic Compounds | 250 |
| | c. | Inorganic Compounds | 252 |
| | **4.** | **Antitrematodal Drugs** | |
| | a. | Drugs Against Adult Flukes | 253 |
| | b. | Drugs Against Immature Flukes | 256 |
| | c. | Drugs Against Immature and Mature Flukes | 256 |

| | | |
|---|---|---|
| | d. Drugs in Paraamphistomiasis | 257 |
| | e. Drugs in Paragonimiasis | 257 |
| | EXERCISE | 257 |
| Chapter 40 | **ANTIPROTOZOAN DRUGS** | |
| | **1. Anticoccidial Drugs** | |
| | a. Drugs in Avian Coccidiosis | 261 |
| | b. Treatment of Bovine Coccidiosis | 264 |
| | c. Treatment of Ovine and Caprine Coccidiosis | 264 |
| | d. Treatment of Rabbit Coccidiosis | 264 |
| | e. Treatment of Canine Coccidiosis | 264 |
| | **2. Antibabesial Drugs** | 265 |
| | **3. Antianaplasmic Drugs** | 266 |
| | **4. Antitheilerial Drugs** | 266 |
| | **5. Trypanocidal Drugs** | 267 |
| | **6. Antimalarial Drugs** | 268 |
| | **7. Treatment of Other Protozoan Diseases** | |
| | a. Antihistomonials | 270 |
| | b. Drugs in Giardiasis, Trichomoniasis, Amoebiasis and Balantidosis | 271 |
| | EXERCISE | 271 |
| Chapter 41 | **ECTOPARASITICIDES** | 274 |
| | EXERCISE | 276 |
| Chapter 42 | **INDIGENOUS DRUGS** | 278 |
| | EXERCISE | 281 |
| | **SECTION VI: TOXICOLOGY** | |
| Chapter 43 | **GENERAL TOXICOLOGY** | |
| | 1. Historical Background | 282 |
| | 2. Scope of Veterinary Toxicology | 282 |
| | 3. Definitions | 282 |
| | 4. Causes or Sources of Poisoning | 283 |
| | 5. Classification of Toxicants/Poisons | 284 |
| | 6. Mode of Action of toxicants | 285 |
| | 7. Toxicokinetics | 285 |
| | 8. Types of Toxicity | 285 |
| | 9. Factors Modifying Toxicity | 286 |
| | 10. General Principles of Diagnosis and treatment of Toxicity | 288 |
| | EXERCISE | 288 |
| Chapter 44 | **TOXICITY OF METALS** | |
| | 1. Arsenic | 291 |
| | 2. Mercury | 292 |
| | 3. Lead | 293 |
| | 4. Copper | 294 |
| | 5. Molybdenum | 295 |
| | 6. Selenium | 295 |
| | 7. Cadmium | 296 |
| | EXERCISE | 297 |
| Chapter 45 | **TOXICITY OF NONMETALS** | |
| | 1. Fluorine | 299 |
| | 2. Nitrates/Nitrites | 299 |
| | 3. Oxalates | 300 |
| | 4. Salt | 301 |
| | 5. Urea | 302 |
| | EXERCISE | 302 |
| Chapter 46 | **TOXICITY OF AGROCHEMICALS** | |
| | 1. Insecticides | 304 |
| | 2. Herbicides | 306 |
| | 3. Fungicides | 307 |
| | 4. Fumigants | 307 |
| | 5. Rodenticides | 308 |
| | EXERCISE | 309 |

| | | | |
|---|---|---|---|
| Chapter 47 | | **PLANT POISONING** | |
| | 1. | Cyanogenetic Plant Poisoning | 312 |
| | 2. | Photosensitization | 313 |
| | 3. | Other Common Plant Toxicities (*Abrus, Calotropis, Datura, Ipomoea, Lantana, Nerium, Thevetia/Cerebera, Parthenium, Pteridium, Ricinus, Strychnos* and *Argemone* spp.) | 314 |
| | 4. | Miscelaaneous Toxic Plants (*Veratrum* spp, *Mellilotus* spp, *Allium cepa, Ipomoea batatus, Jatropha curcas, Tribulus terristris, Glycina max, Medicago sativa and Trofolium repens)* | 317 |
| | EXERCISE | | 318 |
| Chapter 48 | | **TOXINS** | |
| | 1. | Mycotoxins | 320 |
| | 2. | Bacterial Toxins | 323 |
| | 3. | Zootoxins: Snake Venoms | 324 |
| | 4. | Other Zootoxins | 325 |
| | EXERCISE | | 327 |
| Chapter 49 | | **ENVIRONMENTAL TOXICOLOGY** | |
| | 1. | Food Toxicants | 330 |
| | 2. | Feed Additives | 330 |
| | 3. | Indices of Levels of Toxicants in Feeds | 330 |
| | 4. | Common Toxicants in Animal Feeds | 331 |
| | 5. | Feed Additive Toxicity | 332 |
| | 6. | Environmental Pollution | 333 |
| | 7. | Radiation Hazards | 336 |
| | 8. | Chemical Warfare Agents | 337 |
| | EXERCISE | | 338 |
| Chapter 50 | | **DOPING, EUTHANASIA AND DRUG TOXICITY** | |
| | 1. | Doping | 341 |
| | 2. | Euthanasia | 341 |
| | 3. | Drug Toxicity | 342 |
| | EXERCISE | | 343 |

# SECTION I: GENERAL PHARMACOLOGY

## Chapter – 1 : INTRODUCTION

### 1. HISTORICAL BACKGROUND

Drug is derived from a French word *drogue*, meaning 'a dry herb'. Incidentally majority of drugs in ancient times were of plant origin. The oldest writings of medicinal agents belonged to ancient India, closely followed by Chinese and Egyptian literatures. The Rigveda (one of the four Vedas) the oldest records of civilization (3000 BC) described the value of medicinal herbs. Ayurveda, the oldest system of medicine, which is very popular in these days also, recommends herbal remedies and animal origin products for treatment of diease in man and animals. The great Aryan civilization saw the development of both medical and veterinary ayurveda. The ancient physicians, Charaka, Sushruta and Vagbhata pioneered in ayurveda. Nakula, one of the Pandavas followed sound principles of animal husbandry and veterinary science. The ancient Chinese herbal materia madica 'Pen Tsao', written by Emperor Shennung (2735 – 2700 BC) contained many vegetable, metallic and animal products as remedies. The ancient Egyptian medicinal treatises Kahun Papyrus (2000 BC) and Ebers Papyrus (1550 BC) were collections of many herbal prescriptions used by the ancient Egyptians.

The Hippocratic School of Physicians (460 – 375 BC) advocated little use of drugs, but attempted to treat diseases based on four elements of nature (water, fire, air and earth). Aristotle (384 – 322 BC) gave scientific basis of medicine. His student Theopharstus (380 – 287 BC) classified medicinal herbs according to their properties. First Materia Medica was written by Dioscorides (77) describing herbs, minerals and animal products as medicinal preparations. Galen (131 – 201) advocated use of many herbal preparations (polypharmacy), which subsequently became popular as galenical preparations and adopted for centuries to follow.

The fall of Roman Empire paved the way for dominance of Arab/muslim culture which had a great influence on medical field. They developed the art of pharmacy and standardized procedures for preparations of herbal extracts, including alcohol and medicinal agents from natural elements and minerals. The Swiss physician-Chemist Paracelsus (1493-1541) was the first to suggest that the purpose of chemistry was not to make gold, but to apply the knowledge against treatment of diseases; he emphasized medicine was the purpose of chemistry. The Paracelsus message prompted synthesis of many chemicals for therapeutic use. The accumulation of knowledge in development and methods of preparation of many therapeutic agents necessitated compilation of the information in books, pharmacopoeia. The first pharmacopoeia was compiled by the German Valerius Cordus (1514 – 1544). The Swiss physician von Hohenheim (1493 – 1541) introduced tinctures of several plants (including tincture of opium called Tr. laudanum) and inorganic chemicals (mercury, sulfur, iron, copper, potassium etc) for therapeutic uses. During the next three centuries the drug science took significant strides. Notable landmarks were use of Cinchona bark (Peruvian bark) by Spanish explorers of Peru in treating malaria (1630), discovery of prophylactic immunization against small pox by Edward Jenner, use of digitalis (foxglove) in treatment of dropsy by an British physician William Withering (1783), discovery of hypodermic syringe by Alexander Wood (1853) etc. the subsequent progress in pharmacology was largely due to development in procedures of extraction of active principles from plants and their characterization as a result of advances in medicinal chemistry. A German pharmacist Friedrich Serturner (1783 – 1841), a German pharmacist isolated a narcotic alkaloid from opium and named it as morphine after Greek god of dreams Morpheus). Francois Magendie (1783 – 1855), French physioogist developed experiments to study the action of drugs on animal's body. He studied the effects of IV injection of plant drugs ipecac, morphine, strychnine, quinine etc on animals. He along with his students, Claude Bernard (1813 – 1873) and James Blake (1814 – 1893) gave scientific basis of drug effects, such as dose-response relations, drug actions and its distribution and fate in body, structure-activity relationship etc. Claude Bernard is

egarded as 'father of experimental medicine'. These three pioneering workers are credited for laying the foundations of modern pharmacology. Paul Ehrlich in late 19th century, followed by Langely, Clark and Patan in early 20th century gave the concepts of mode of action of drugs and drug-receptor interaction.

Rudolph Buchheim (1820 – 1879) founded the first Parmacology Laboratory in the University of Dorpat, Estonia in Germany. He is regarded as the 'father of modern pharmacology'. He described the actions of drugs at cellular level in relation to their therapeutic use. His student Oswald Schmiedeberg (1838 – 1921) became the first Professor of Pharmacology at the University of Dorpat. He emphasized pharmacology as a separate discipline as the study of changes in living organisms caused by chemicals. Schmiedeberg later moved to University of Strausberg, where he attracted several students from different parts of the world, including John J. Abel. He was appointed as Professor of Pharmacology in Medical School of University of Michigan in 1890. Later in 1892, he was called to head Pharmacology Lab in Jons Hopkins Medical School, where adrenaline (1902) and acetylcholine (1905) were isolated from adrenal medulla. Abel is regarded as 'father of American pharmacology' who started the Journal of Experimental Pharmacology and Therapeutics.

## 2. DEFINITIONS AND BRANCHES OF PHARMACOLOGY

**Pharmacology**: Derived from two Greek words 'Pharmacon' and 'Logos' meaning drug and science respectively: Science of drugs. It may be defined as the science of study of sources, properties (physical and chemical); administration, absorption, distribution, metabolism and excretion; effects (physiological and biochemical); uses and toxicity of drugs. The various branches or sub-disciplines of pharmacology include:

**Materia Medica**: It refers to medicinal materials and includes study of sources, properties, compounding (preparation), dispensing and uses of medicinal preparations for the treatment of diseases.

**Pharmacognosy**: Study of sources and identification (origin) of drugs.

**Pharmacokinetics**: Study of absorption, distribution, metabolism and excretion of drugs: How the animal's body affects the drugs (from the Greek Kinesis meaning movement). Change in concentration of drugs in the body.

**Pharmacometrics**: Study of qualitative and quantitative aspects of drug effects in lab animals. It deals with measurement of drug responses.

**Metrology**: It is the science of weights and measures used in pharmacy.

**Pharmacy**: It refers to collection, preparation, standardization and dispensing of drugs in different dosage forms.

**Pharmacodynamics**: Study of physiological and biochemical effects and mechanism of action of drugs: How drugs affect the animal's body (From the Greek Dynamics meaning power). It is the response of an organism to drugs in the absence of disease.

**Pharmacotherapeutics**: Study of drug effects in disease states. It is the response of an organism to drugs in disease condition.

**Veterinary Clinical Pharmacology**: Clinical evaluation of a new drug for use in animals.

**Comparative Pharmacology**: Study of variation in drug effects in different species of animals.

**Experimental Pharmacology**: Study of effects and mechanism of drug action of drugs under laboratory conditions (usually in lab animal model).

**Applied Pharmacology**: It is the study of drug effects in disease in relation to normal condition.

**Chemotherapy**: The branch of Pharmacology which deals with use of therapeutic agents in treatment of diseases caused by pathogens. The chemotherapeutic agents selectively destroy or inhibit the pathogens (viruses, bacteria, fungi and parasites).

**Toxicology**: Originally the science of poisons (Greek words 'Toxicon' = Poison; 'Logos' = Science). It includes study of toxicity or adverse effects of drugs or chemical, physical and biological agents in man and animals.

**Neuropharmacology**: Branch of pharmacology which deals with the study of actions and effects of drugs on nervous system. It is the study of effects of drugs on nerve function.

**Immunopharmacology**: Branch of pharmacology which deals with study of drug-induced immunomo-dulation and immunosuppression.

**Molecular Pharmacology**: It is the study of chemical interaction between drug molecules and the chemical groups in cells in explaining the mechanism of drug action and the effects observed. Drug molecules must react with biomolecules in cells (receptors) in exerting their effects.

**Pharmacoepidemiology**: It is the study of drug effects at population level, in order to identify the variations in drug response between individulas in a population and/or groups of population.

**Pharmacoeconomics**: It deals with quantification of therapeutic use of drugs in relation to the cost of treatment. It helps in arriving at the economics of drug use and the derived benefits.

Both pharmacoepidemiology and pharmacoeconomics deal with the therapeutic outcome of usage of drugs at population level.

Advancement in molecular biology especially the recombinant DNA technology and emergence of biotechnology has opened new chapters in pharmacology such as pharmacogenetics, pharmacogenomics, gene therapy and biopharmaceuticals.

**Pharmacogenetics**: It is the study of genetic influences on drug responses. Study of genetically-mediated variations in drug responses.

**Pharmacogenomics**: It is the study of prediction of drug responses between individulas based on their genetic makeup.

**Drug**: It is defined as an agent, of chemical, physical or biological origin, intended for treating, prevention or diagnosis of disease in man and animals.

**Prodrug**: It is a drug after metabolic activation produces the therapeutic effect, where the parent drug molecule is ineffective or inert, but its metabolite is pharmacologically active.

**Placebo**: It is a Latin word, meaning 'I may please you'. It is referred to an agent/substance/preparation consisting of an inert pharmacological agent (dummy drug) to simulate the real drug therapy in exerting psychological impact of medication in human subjects. A placebo is usually given to a human patient with imaginary illness. Clinical pharmacological study of a new drug invariably includes parallel placebo treatment goup.

**Dose**: It is the amount of drug administered to a patient in order to produce the desired therapeutic effect and expressed as quantity per unit body weight (mg/kg). The dose may have to be repeated once, twice or thrice in a day or needed to be continued for days, depending upon the necessity.

**Posology**: Study dealing with drug dosage determination.

## 3. DRUG DEVELOPMENT, SCREENING AND NOMENCLATURE

Drug development refers to design, synthesis and introduction of chemicals/other agents as therapeutic agents i.e. as drugs, for treatment of diseases in man, birds and animals. In older times, plants to a great extent and minerals or animals to a limited extent constituted the major sources of therapeutic agents. Even today, several herbal remedies are still used under the Indian system of medicine (*Ayurveda*). Many of the present day wonder drugs like morphine, cocaine, digitalis, quinine, reserpine, atropine, d-tubocurarine, vincristine, vinblastine, emetine etc are of plant origin. Some of these are still extracted from plant sources. Efforts are vigorously pursued to find out new potential therapeutic chemicals from several Indian plants like *Azadirachta indica, Curcuma longa, Withania somnifera, Asperagus racemosus* etc. Many substances of fungal origin continue to be sources of highly effective antiinfective agents (antibiotics).

With the advancement of knowledge in organic chemistry and synthetic processes, the plant drugs and the natural antibiotics are purified, chemically identified and synthesized in the laboratory. Understanding of chemical structure of such therapeutic agents and their chemical structure-activity (pharmacological) relationship helped in synthesis of a host of analogues, derivatives or semisynthetic compounds with better therapeutic index and/or specific target-oriented pharmacological/therapeutic actions and antidotes for counteracting their adverse effects or toxicity.

The government and its agencies (FDA, Drug Controller of India etc) control the introduction of new drugs for mass scale clinical use through strict laws or legal enactments (Food, Drug and Cosmetics Act, Insecticide Act etc.). The WHO also provides guidelines for introduction and use of new therapeutic agents. The various stages in new drug development can be conveniently divided into different phases:

**Phase I: New Drug Discovery**: The drug candidate molecules selected are subjected to extensive pharmacodynamic screening adopting standard experimental pharmacology techniques consisting of approved laboratory animal models and/or *in vitro* techniques (protocols). This helps in identifying the potential drug molecule based on detailed pharmacological profiling. A pharmaceutical/organic chemist and a pharmacologist help in achieving this purpose.

**Phase II: Pre-clinical Evaluation**: During this stage exhaustive safety evaluation of the drug candidate is carried out. The drug candidate is subjected to short term toxicity testing and to assess adverse effects, if any, on all systems of the body and generation of pharmacokinetic data in different species of lab animals as recommended in the protocols. All the studies and testing should invariably be in strict compliance to good laboratory practice (GLP). During this phase, feasibility for large-scale synthesis and purification of the drug candidate and its formulation in required dosage form and suggested dosage regimen as required for clinical evaluation are arrived. Long term toxicity testing in lab animals as per the protocol must also be initiated in this phase (to be continued in the next phase). The investigator-team of this phase may include a clinical pharmacologist, a toxicologist, a biochemist, a pathologist and a pharmaceutical chemist.

**Phase III: Clinical Evaluation**: The long-term toxicity evaluation and testing of the drug-candidate for special toxicities like teratogenecity, carcinogenecity, immunotoxicity, genotoxicity, reproduction toxicity etc are completed. Further investigations of this phase may be considered in different stages:

**Stage I**: The drug candidate is assessed for its tolerability, side effects if any, interactions with other drugs and pharmacokinetics in small groups of healthy subjects. In addition, this phase also includes study of the efficacy and safety of the drug-candidate in small groups of patients with hepatic or renal impairment.

**Stage II**: The drug-candidate is evaluated for therapeutic efficacy, dose range and pharmacokinetics in small groups of selected patients.

**Stage III**: This stage includes conduct of large scale controlled clinical evaluation of the drug-candidate for its safety and efficacy in large groups of patients.

The entire data of evaluation in all the above phases is then submitted to the appropriate Drug Regulatory Authority/Body for approval and registration of the new drug-candidate. After the necessary approval only the drug-candidate is recognized as a "new drug" and it is allowed/licensed for marketing in the country. All the investigations/clinical evaluation are conducted and supervised by experienced Clinical Pharmacologists and Toxicologists.

**Phase IV: Post-marketing Monitoring**: This phase is concerned with continued surveillance of utilization pattern of the new drug and to record any previously unknown adverse or beneficial effect. If any adverse effect is detected due to the new drug, the authority can cancel its approval and the drug will be banned and withdrawn from the market.

The drug development (from synthesis up to the time it is permitted for marketing) is a very lengthy process, involving expenditure of huge amounts of money. An estimate points out an expenditure of 250 to 500 million British Pounds over a period of 8 to 12 years in successful entry of one compound as new drug in market. It is also indicated that out of twelve compounds entering the first phase of development only one new drug succeeds in reaching the last phase i.e. market.

**Drug Screening**

It refers to study of chemicals or other substances (extracts, fluids etc) in order to evaluate their pharmacological activity - pharmacodynamic properties. The objective of drug screening is to fnd out the true pharmacologically active drug candidate for a given effect. Three types of procedures are followed for screening:

1. **Simple Screening**: it involves testing of a chemical/drug candidate for one or two specific predetermined pharmacological activity (blood glucose levels for hypoglycaemic activity; zone of inhibition of bacterial growth for antibacterial drugs etc).
2. **Programmed Screening**: It consists of screening the test agent/drug candidate or of a series of chemically related compounds as per a battery of pharmacological tests (antihypertensive drugs on cardiovascular system: blood vessels, heart rate, cardiac out put, blood flow in vessels, BP etc).
3. **Blind Screening**: This procedure is adopted when there is no prior pharmacological or chemical knowledge of the test compound (a new compound). Usually, the test material is subjected to extensive pharmacological screening to identify its effects on different systems of the body. This helps in identifying the pharmacological utility of the test agent. If found to possess useful pharmacological activities, the drug candidate will be subjected to simple or programmed screening.

**Drug Nomemclature**

Every day new drugs are synthesized, screened, marketed and added to the endless list of drugs. Often the drugs are in market with varied brand/proprietary/trade names (marketed by different national/international pharmaceuticals, creating a state of confusing situation, especially to the physician/veterinarian or the consumer/owner of the animal. The phrase 'therapeutic jungle' is used by some to explain the situation. A drug in its process of introduction is assigned different names.

When a new drug is synthesized, it is first assigned a code name or number (usually identifying with its inventor, manufacturer/pharmaceutical company). If it is found promising after clinical evaluation, the manufacturer wants to put in the market, the new drug is given a generic name to designate its pharmacological class (nonproprietary name). If the new drug gets official recognition by drug regulatory authority, ts manufacturer gives it a proprietary or trade name. The trade name is more easily pronounceable and rememberable than the complex chemical name or the generic name. The chemical name indicates the chemical nature of the drug. The examples are:

| Chemical Name | Nonproprietary/Generic Name | Proprietary Name |
|---|---|---|
| 3, 4-Dihydroxyphenylethanolmethyl amine | Epinephrine | Adrenaline |
| Beta-phenylisopropylamine | Amphetamine | Benzidrine |
| Acetylsalicylic acid | Aspirin | Ecosprin |

**Pharmacopoeia**

It is a drug compendium consisting of officially recognized drug preparations/formulations. It gives the information on source, properties, purity, potency of recognized drugs and tests for their identity. A pharmacopoeia is the official publication of drug standards. It is revised periodically for the purpose of deletion of old drugs with proven ineffectiveness and/or adverse effects upon usage and for addition of new drugs. The important pharmacopoeias are:

| | | |
|---|---|---|
| IP | : | The International or the Indian Pharmacopoeia |
| USP | : | The United States Pharmacopoeia |
| BP | : | The British Pharmacopoeia |
| BPC | : | The British Pharmaceutical Codex |
| EP | : | European Pharmacopeia |
| I Vet. P | : | The Indian Veterinary Pharmacopoeia |

Brit C = British reference book,
USPDI = United States pharmacopoeia dispensing information.

1) from old book - & conform.



| | | |
|---|---|---|
| NF | : | The National Formulary (USA) |
| NF | : | The National Formulary of India |
| BNF | : | The British National Formulary |
| NND | : | The New and Nonofficial Drugs |
| ADR | : | The accepted Dental Remedies |

The USD (United States Dispensatory) is a compilation of all drugs included in USP, BP, IP, NF etc.
The PDR (Physicians Desk Reference) also serves the source of information on drugs in use.
The abbreviation of the pharmacopoeia is mentioned after the name of the drug: Tr. Iodine IP i.e. the tincture of iodine corresponding (in properties, purity, strength etc) to the standard tincture iodine mentioned in the Indian Pharmacopoeia.

## 4. Scope of Veterinary Pharmacology

The Veterinary Pharmacology (VP) refers to application of the science of pharmacology for the benefit and well being of different species of animals, including the birds. Hence, due to species variation (ruminants, non-ruminants & birds) the scope of VP is very wide as compared to medical pharmacology which deals with the only one species i.e. man. The Veterinarian has the responsibility of health care of all animals, except man. Species variation is the essence of VP.

### EXERCISE

1. Give a brief account of historical background of pharmacology.
2. What are the major landmarks in development of pharmacology?
3. **Write a short note on the following**:
   a. Ancient literature on herbal remedies
   b. Drug development
   c. Drug screening
   d. Drug nomenclature
   e. Pharmacopoeia
4. **Differentiate between the following**:
   a. Pharmacy & Pharmacology
   b. Metrology & Meteorology
   c. Pharmacokinetics & Pharmacodynamics
   d. Pharmacometrics & Pharmacodynamics
   e. Pharmacodynamics & Pharmacotherapeutics
   f. Drug & Prodrug
   g. Drug & Placebo
   h. Pharmacology & Pharmacognosy
   i. Simple screening & Programmed screening
   j. Blind screening & Programmed screening
   k. Generic name & Trade name
   l. Materia medica & Pharmacology
5. **What do you mean? or Define the following**:
   a. Ayurveda
   b. Drug
   c. Prodrug
   d. Placebo
   e. Pharmacy
   f. Materia medica
   g. Pharmacology
   h. Pharmacognosy
   i. Galenicals
   j. Polypharmacy
   k. Pharmacometrics
   l. Pharmacodynamics
   m. Pharmacokinetics
   n. Pharmacotherapeutics
   o. Comparative pharmacology
   p. Clinical pharmacology
   q. Pharmacoepidemiology
   r. Pharmacoeconomics
   s. Pharmacogenetics
   t. Pharmacogenomics
   u. Metrology
   v. Dose
   w. Psology
   x. Toxicology
   y. Chemotherapy
   z. Immunopharmacology
   aa. Drug screening
   bb. Pharmacopoeia
   cc. Therapeutic jungle
   dd. Blind screening
   ee. Programmed screening
   ff. Simple screening
   gg. Ebers Papyrus
   hh. Kahun Papyrus
   ii. Pen Tsao
   jj. Dummy drug
6. **For what the following persons are remembered for?**
   a. Galen
   b. Alexander Wood
   c. Nakula
   d. Charaka
   e. Shshruta
   f. William Withering
   g. Serturner
   h. Edward Jenner
   i. Shennung
   j. Francois Magendie
   k. Claude Bernard
   l. James Blake
   m. Paul Ehrlich
   n. Paton
   o. Clark

p. Buchheim
q. Schiemedeberg
r. Abel
s. Aristotle
t. Theophrastus
u. Valerius Cordus
v. Von Hohenheim

7. **Give the full form of the following**
a. IP
b. USP
c. BP
d. B Vet C
e. I Vet P
f. NF
g. BNF
h. NND
i. ADR
j. USD
k. PDR

8. **Match the pairs**
a. Ayurveda : Science of life/Indian System of Medicine
c. Pen Tsao : Chinese Materia Medica
d. Valerius Cordus : First Pharmacopoea
e. Von Hohenheim : Tr. of opium
f. Edward Jenner : Small pox vaccine
g. Withering : Digitalis/fox glove
h. Serturner : Morphine
i. Francois Megendie : Experi'ntal Pharmacology
j. Claude Bernard : Experi'ntal Pharmacology
k. James Blake : Experi'ntal Pharmacology
b. Eber's / Kahun Papyrus : Egyptian Materia Medica
l. Paul Ehrlich : Receptor concept
m. Langeley : Receptor concept
n. Paton/Clarke : Drug-Receptor Interaction
o. Buchheim : First Pharmacology Lab.
p. Schiemederg : First Pharmacology Professor
q. Abel : Father of American Pharmacology
r. Aspirin : Generic name
s. Adrenaline : Trade name

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# Chapter – 2 : SOURCES, CLASSIFICATION AND ADMINISTRATION OF DRUGS

## 1. Sources of Drugs

Drugs are obtained from several sources (Classification of drugs):

1. Plant Origin
2. Animal Origin
3. Microbial Origin
4. Mineral Origin
5. Synthetic Origin
6. Semisythetic Origin
7. Therapeutic Genes
8. Biopharmaceuticals

**Plant Drugs**:

The ancient or original sources of drugs are the plants, collectively called as medicinal plants. All parts of the medicinal plants such as root, rhizome, tubers, stem, bark, flowers, fruits and seeds have therapeutic values.

Root: Belladonna, Sarpagandhi
Corn (fleshy underground stem): Shatawari
Rhizome: Ginger, Haldi
Wood: Sandal wood
Bark: Acacia, Catechu, Cinnamon, Cinchona
Leaves: Atropine, Cocaine, Physostigmine
Flowers: Digitalis, Hibiscus, Chrysanthemum
Fruits: Anise, papaya
Seeds: Nuxvomica, Kalimirchi, methi
Secretions: Opium, Gums, Aloe.

The extracts or other preparations of parts of medicinal plants are considered as crude form of the drugs. However, the original plant parts are still used in making medicines under Ayurvedic system of Indian medicine (see historical background).

**Drugs from Animal Sources**:

a) Hormones: Posterior pituitory extract/oxytocin, insluin, thyroxine, gonadotrophins
b) Vitamins: Cod or shark liver oil as a rich source of vitamins A and D
c) Antisera: Canine distemper antisera and antisnake venom
d) Others: Heparin, liver extract, immunoglobulins, and blood/plasma

**Drugs from Microbial Sources**: Fungi/actinomycetes and bacteria as the source of antibiotics (penicillin, streptomycin, gentamicin, neomycin etc). Viruses/bacteria in preparation of vaccines. Dried yeast as an important source of B-complex vitamins.

**Drugs of Mineral origin**: Inorganic salts in treatment or prevention of disease states.

Antacid: Magnesium oxide
Expectorant: Potassium iodide
Haematinic: Ferrous sulfate
Purgative; Magnesium sulfate
Diuretic: Potassium nitrate
Hypothyroidism: Iodine

Mineral Oil: Mixtures of hydrocarbons methane and related solvents, obtained by fractional distillation of petrol. Examples are: Liquid paraffin (laxative, long term use interferes with absorption of Vitamins A and D, Ca and P), Soft paraffin and hard paraffin (Vehicles for making creams or ointments for application on skin). These resemble fat in appearance, are insoluble in water, but soluble in ether or chloroform.

**Synthetic Drugs**: Through chemical synthesis (antipyretics, barbiturates, anti-inflammatory drugs, tranquilizers, anaesthetics, antiseptics, antiprotozoan drugs, antihistamines etc). Majority of current day drugs are from synthesis in the laboratory.

**Semisynthetic Drugs**: These are produced by chemical alteration of natural origin drugs (derivatives and antagonists of morphine, dihydrostreptomycin from streptomycin and semisynthetic penicillins from natural penicillin).

**Gene Therapy**: It means prevention or treatment of diseases through manipulation of gene function. It is insertion of specific genes (therapeutic genes) exogenously into the animal cells. The concept of gene therapy has its origin from the fact that manipulation of gene expression could change the function of abnormal cells as manifestation/malfunction of an existing gene, and thus the course of a disease. It involves replacing the defective gene or supplementation to a nonfunctional gene or suppression of an abnormal gene. Recombinant DNA technology forms the basis of synthesis of therapeutic genes.

Gene delivery into host is highly complicated and different from that of conventional drug delivery systems. The process involves inserting a therapeutic gene first into a *vector* (Viral Vectors: Retro-or Adenoviruses or Nonviral Vectors: Liposomes, microspheres and plasmid DNA). A vector with the gene is then introduced into the patient through either *in vivo* or *ex vivo* means. The *in vivo* means involves injecting the suspension of the vector having the therapeutic gene intravenously or into the target tissue/organ. The *ex vivo* method involves first inserting the therapeutic gene into stem cells obtained from the patient (blood or bone marrow) and inject the same into the patient.

Gene therapy is currently aimed at treatment of diseases not responding to conventional drug therapy, such as inherited metabolic diseases through either correction of a deficiency or blockade of an abnormal metabolic reaction. It is also applied to induce synthesis of a deficient protein in the host cells and treatment of a variety of cancers (melanoma, renal carcinoma, lung cancer, cystic fibrosis etc), certain immune deficiencies and infectious diseases (like HIV).

**Biopharmaceuticals**: These are therapeutic agents produced through biotechnological means, but not by conventional laboratory (chemical) synthesis. The principle of biopharmaceuticals and the process of their development have origin from the advancement in the knowledge of molecular cell biology and biotechnology. Therefore, biopharmaceuticals popularly called as "Designer Proteins" are the promising therapeutic tools of the future. Examples of biopharmaceuticals include functional human peptides (ADH, oxytocin, GnRH, ACTH, TSH/TRH, Calcitonin, Insulun, Somatostatin, Growth Hormone, Cyclosporin etc.) and enzymes/proteins (Streptokinase, Asparaginase, DNAase, glucocerebrosidase, erythropoietin, Clotting Factors, Interferons, Monoclonal Antibodies, Antibodies, Vaccines etc.). Daclizumab (Zenopox), genetically engineered human IgG (immunosuppressant monoclonal antibody binds specifically to α-chain of $IL_2$ receptor) used to lower the rate of rejection phenomenon in kidney transplant recipients. Through DNA recombinant technology, bacteria are induced to produce hormones like insluin and growth hormone and enzymes like L-asparaginase.

## 2. Active Principles of Medicinal Plants (AG, OG, OR, ST)

The medicinal value of plants or the crude preparations of medicinal plants is due to presence of a variety of pharmacologically active principles such as alkaloids, glycosides, oils, resins, oleoresins, gums, saponins and tannins.

**Alkaloids**: Basic nitrogenous substances insoluble in water and less soluble in alcohol and soluble in ether, chloroform and oils. They form water soluble crystalline salts with acids. Alkaloids consisting of oxygen are solids (Atropine, reserpine, emetine, morphine, strychnine and quinine). Alkaloids without oxygen are liquids (Nicotine, pilocarpine and lobeline). The important alkaloids along with their source and major pharmacological action are as under:

| Sr. No. | Alkaloid | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Atropine | *Atropa belladonna* | Cholinergic/Muscarinic blocker |
| 2 | Arecoline | *Areca catechu* | Cholineric alkaloid |
| 3 | Caffeine | *Coffee Arabica* | Cortical/CVS stimulant |
| 4 | Cocaine | *Erthroxylon cocoa* | Local anesthetic/CNS excitation |
| 5 | Colchicine | *Colchicum autumnale* | Anti-inflammatory (gouty arthritis) |
| 6 | Emetine/Cephaline | *Cephalis ipecauanha* | Reflex vomition (GI irritation) |
| 7 | Ephedrine | *Ephedra vulgaris* | Indrect acting sympathomimetic |
| 8 | Epinephrine | *Adrenal medulla* | Sympathomimetic/Cadiac stimulant |
| 9 | Ergometrine | *Claviceps purpurea* | Oxytocic/Alpha-adrenoceptor blocker |
| 10 | Leptadine | *Leptadenia reticulate* | Galactagogue |
| 11 | Lobeline | *Lobelia inflate* | Ganlionic stimulant/blocker |
| 12 | Morphine | *Papaver somniferum* | Narcotic analgesic |
| 13 | Muscaine | *Anamita muscaria* | Muscarinic agonist |
| 14 | Nicotine | *Nicotiana tobaccum* | Ganglionic stimulant/blocker |
| 15 | Physostigmine | *Physostigma venunosum* | Anticholinesterase |
| 16 | Pilocarpine | *Pilocarpus jobarandi* | Cholinergic |
| 17 | Quinine | *Cinchona officinals* | Antimalarial |
| 18 | Reserpine | *Rauwolfia serpentine* | Antihypertensive |
| 19 | Somniferine | *Withania somniera* | Immunostimulant/Antistress/Adoptogenic |
| 20 | Strychnine/Brucine | *Strychnus nuxvomica* | Spinal stimulant/Convulsant |

**Glycosides**: Compounds containing a sugar (glycone) and nonsugar (aglycone) parts joined together through an ether-like linkage ($C_2H_5$-O-$C_2H_5$). The pharmacological action is in aglycone (genin) part and the glycone (sugar) part determines its solubility, tissue permeability and duration of action of aglycone. They do not form salts with acids. On acid or alkali and enzyme hydrolysis, the glycoside breaks into the two parts. The glycosides and their sources are:

| Sr. No. | Glycoside | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Digitoxin/gitoxin/ / digoxin or gitalin | Leaves of *Digitalis lanata/ purpurea* | Cardiotonic |
| 2 | Strophanthidin | Seeds of *Strophanthus kombe* | Cardiotonic |
| 3 | Ouabain | Bulb of *Urgenia maritime* | Cardiotonic |
| 4 | Neriosid/Oleandrin | Leaves/seeds of *Nerium oleander/ indica* | Cardiotoxic |
| 5 | Cereberin | Seeds of *Cerebera thevetia* | Cardiotoxic |
| 6 | Amygdalin | Fruit of *Prunus amygdalus* | Cyanogenic |
| 7 | Dhurrin | Immature stocks of *Sorghum vulgare* | Cyanogenic |
| 8 | Linamarin | Immature seeds of *Linum usitatissimum* | Cyanogenic |
| 9 | Aloin/barblin | Leaves/stem of *Aloe vera* | Wound healing/Antibacterial |
| 10 | Kutkin | Leaves of *Picrorhiza kurroa* | Hepatoprotective |
| 11 | Glycerrhizin | Stem of *Glycerrhiza glabra* | Axinolytic/Anti-inflammatory |
| 12 | Mangeferin | Fruit/Leaves of *Mangifera indica* | Hepatoprotective/Antoxidant |
| 13 | Swertiamarin | Stem/Leaves of *Swertia chirata* | Cardiotonic/Hepatotonic |

**Oils**: Are of two types:

**Fixed Oils**: These are glycerides of oleic, palmitic and stearic acids. Many fixed oils have food value i.e cooking oils (Corn oil, GN oil, sun flower oil, mustard oil, soybean oil, coconut oil, palm oil) which are pharmacologically inert and serve as vehicle for administration of fat soluble drugs, but some others have pharmacological actions (excess ingestion of food oil also causes purgation) — easy evacuation of bowel - mg

| Sr. No. | Fixed oil | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Castor oil | Dried seeds of *Ricinus communis* | Purgative |
| 2 | Linseed oil | Dried seeds of *Linum usitatissium* | Demulcent/vehicle/purgative |
| 3 | Croton oil | Dried seeds of *Croton tiglium* | Drastic purgative |

**Volatile Oils**: These have no food value. Are volatile and emit characteristic odour while evaporation (heating). These oils are also called as aromatic, essential or etheral or flavouring oils. Most of these oils have medicinal value:

| Sr. No. | Volatile oil | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Eucalyptus oil | Leaves of *Eucalyptus globules* | Expectorant/Rubefacient |
| 2 | Ginger oil | Rhizomes of *Zingiber officinale* | Stomachic/Carminative |
| 3 | Turpenine oil | Wood of *Cedrus deodara/Pinus deodara* | Counterirritant/Antizymotic |
| 4 | Clove oil | Dried flower heads of *Eugenia caryophyllus* | Analgesic/Antiseptic |
| 5 | Pippermint oil | Flowering tops of *Menha piperata* | Antiseptic/Antiemetic |
| 6 | Asafoetida oil | Rhizome/root of *Ferula foetida* | Carminative/anthelmintic |

**Resins**: Brittle amorphous compounds formed from oxidation or polymerization of terpene components of volatile oils. These are insoluble in water, but soluble in alcohol and other organic solvents: These form soap with alkalies.

| Sr. No. | Resin | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Colophonium | Residue left after distillation of crude turpentine | Antiseptic/Styptic/Astringent |
| 2 | Podophylline | Dried rhizome and root of *Podophyllum emodi* | Purgative/Sialic/Cholagogue/ Antimitotic (anticancer) |

**Oleoresins**: Mixtures of volatile oils, gum and resins:

| Sr. No. | Oleoresin | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Myrrha | Secretion from stem of *Commiphora myrrha* | Astringent/Antiseptic/Stomachic/ Carminative/Expectorant |
| 2 | Asafetida | Secretion from root of *Ferula foetida* | Carminative/Antispasmodic |

Balsams are also considered as oleoresins. These contain an aromatic acid, resin and volatile oil:

| Sr. No | Balsam | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Balsam of Tolu | Secretion from trunk of *Myroxylon toluiferum* | Expectorant/Antiseptic |
| 2 | Balsam of Peru | Secretion from trunk of *Myroxylon pereioe* | Antiseptic/Acaricide |

**Gums**: Are polysaccharide secretary products of plants capable of forming thick mucilaginous colloids when mixed with water. Gums are pharmacologically inert with no systemic effects, but exert demulcent action on surfaces and are mainly used as suspending or emulsifying agents in pharmacy. Agar (a colloidal carbohydrate obtained from sea weeds) acts as a bulk purgative.

| Sr. No | Gum | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Gumacacia | *Acacia Senegal* | Demulcent/Emulsifier |
| 2 | Gumarabica | *Acacia Arabica* | Demulcent/Emulsifier |
| 3 | Gum tragacanth | *Astragalus gummifier* | Demulcent/Emulsifier |

* All abbreviations & meaning see in dictionary.

**Saponins**: Nonnitrogenous substances soluble in water and form foam/froth when shaken with water. Upon hydrolysis split into a sugar part and a nonsugar part (sapogenin), hence considered as a subclass of glycosides. Saponins can also be used as emulsifiers. Saponins cause haemolysis of RBC. (Examples are quillaria, senega).

Tannins: Nonnitrogenous plant constituents having a characteristic astringent action (precipitation of proteins) upon mucous membranes. Exert a protective action on the mucosa (GI) against the irritants. Tannins also inactivate the alkaloidal poisons. These are soluble in water:

| Sr. No. | Tannin | Source | Pharmacological Action |
|---|---|---|---|
| 1 | Catechu | Dried water extract of leaves/young shoots of *Uncaria gambier* | Astringent.Precipitates alkaloids |
| 2 | Kino | Dried juice of trunk of *Pterocarpus Marsupium* | Astringent.Precipitates alkaloids |
| 3 | Galla (Galls) | Excrescences from young twigs of *Quercus infectoria* (Oak) | Astringent/Antiseptic/ antisialic |
| 4 | Homamelis | Dried leaves of *Homamelis virginiana* | Astringent/Hemostatic |
| 5 | Myrobalanum | Dried fruits of *Terminalia chebula* | Astringent/Stomachic/Tonic |
| 6 | Kurchi | Dried bark of *Holarrhena antidysenterica* | Antidysenteric/Antiamoebic/ Astringent |

**Classification of Drugs Based on Chemical Nature:**

1. Organic Drugs: Morphine sulfate, atropine sulfate, digoxin, reserpine, quinine etc.
2. Inorganic Drugs: Sodium chloride, magnesium sulfate/oxide, ferrous sulfate etc.
3. Acidic Drugs: Benzoic acid, acetic acid, salicylic acid, sodium acid phosphate etc.
4. Basic Drugs: Sodium bicarbonate, magnesium hydroxide etc.

### 3. Pharmacotherapeutic Classification of Drugs

**Drugs Acting on Digestive System:**

1. Sialics or Sialagogues : Agents that increase the volume of saliva
2. Antisialics or antisialagogues: Agents that decrease the volume of saliva secretion.
3. Emollients/demulscents: Agents that soothen and protect the GI mucosa against the ingested irritants.
4. Stomachics: Agents that increase gastric secretion.
5. Bitters: Agents that are bitter in taste and increase salivary and gastric secretions (increase appetitie)
6. Antacids: Agents that neutralize the gastric hyperacidity. eg- Magnesium oxide
7. Emetics: Agents that cause vomition.
8. Antiemetics: Agents that prevent vomition.
9. Carminatives: Agents that prevent formation of gases and help in their expulsion from stomach and intestines.
10. Antizymotics: Agents that prevent bacterial fermentation and arrest further gas production in rumen.
11. Purgatives/laxatives: Agents that help in easy evacuation of bowels. eg- Magnesium Sulphate.
12. Astringents: Agents that protect the inflammed intestinal mucosa by precipitating the superficial proteins and help in reducing intestinal irritation and check bleeding.
13. Choleretics: Agents that increase bile formation and secretion.
14. Cholagogues: Agents that help in contraction of gall bladder and increase bile flow into intestines.
15. Hepatotonics: Agents that increase hepatic function.
16. Lipotropics: Agents that help in removal of fat from hepatocytes.

**Drugs Acting on Cardiovascular System:**

1. Haematinics: Agents that increase the formation of haemoglobin in RBC. eg- Ferrous Salphate – mineral category
2. Haemostatics/Styptics: Agents that arrest/stop bleeding.
3. Coagulants: Agents that promote blood clotting.
4. Anticoagulants: Agents that prevent blood coagulation.
5. Cardiac depressants/Antiarrhythmics: Agents that prevent cardiac arrhythmia.
6. Vasoconstrictors: Agents that increase BP through constriction of blood vessels.
7. Vasodilators: Agents that decrease BP through dilatation of blood vessels.
8. Antihypertensives: Agents that decrease the elevated BP.
9. Antiangina drugs: Agents that promote coronary blood circulation and prevent cardiac arrest.
10. Cardiac stimulants: Agents that stimulate the contraction of a failing heart.
11. Cardiotonics: Agents that reduce size of enlarged heart by increasing the force of myocardial contraction, without much increase in corresponding oxygen consumption by myocardium.

**Drugs Acting on Urogenetinal System:**

1. Diuretics: Agents that promote formation and excretion of urine. eg- Potassium nitrate
2. Aphrodisiacs: Agents that increase sexual urge and libido.
3. Anaphrodisiacs: Agents that lower sexual desire and libido.
4. Ecbolics/Oxytocics: Agents that cause contraction of uterus and expel its contents.
5. Galactagogues: Agents that increase milk secretion
6. Emmenagogues: Agents that help in appearance of 'heat' in animals or regulate oestrous cycle.
7. Tocolytics: Drugs that relax the uterus.

**Drugs Acting on Respiratory System:**

1. Expectorants: Drugs that promote fluidity and help to expel bronchial secretions. eg- Potassium iodide.
2. Bronchodilators/Bronchial antispasmodics: Drugs that relax bronchial smooth muscles, dilate respiratory passages and relieve bronchial spasm.
3. Analeptics: Drugs that cause stimulation of depressed respiration (respiratory stimulants).
4. Antitussives (Cough sedatives): Drugs that suppress cough.

**Drugs Acting on Nervous System:**

1. Anaesthetics: Agents that cause reversible loss of consciousness or sensations (pain in surgery).
2. Analgesics: Drugs that cause relief of pain or suppress pain sensation, without altering consciousness.
3. Narcotics: Agents that cause deep sleep
4. Hypnotics: Drugs that cause a condition similar to normal sleep.
5. Sedatives: Drugs that reduce CNS excitation without inducing sleep (mild CNS depression).
6. Tranquilizers: Drugs that calm down an excited animal (ataraxia: Ataractics).
7. Anticonvulsants: Drugs that counteract convulsions or CNS hyperexcitability.

**Drugs Acting on Metabolism:**

1. Antipyretics: Drugs that lower the elevated body temperature (fever).
2. Anabolics: Drugs that promote weight gain and physical performance.
3. Alteratives: Agents that modify tissue metabolism (nutrition) and function of the organs.

**Drugs Acting on Skin:**

1. Diaphoretics: Drugs that increase sweating.
2. Anhydrotics: Agents that decrease sweating
3. Depilatories: Agents that remove superfluous hair (unwanted)
4. Counter irritants: Agents that are applied through rubbing on the skin (massage) and promote healing and aid in relieving pain in tissues beneath the skin.

5. Keratolytics: Agents that are used to destroy excessive granulation growth on the skin (warts) or in treatment of hyperkeratosis.
6. Caustics: Agents that cause death of the tissue.
7. Refrigerants: Agents that cause coolness of the areas of contact.
8. Antipruritics: Agents that reduce irritation and itching.
9. Detergents: Agents that are used as cleansing agents.
10. Deodorants: Agents that eliminate or mask unpleasant odours.
11. Emollients: Agents used to soothen, lubricate and protect the skin.
12. Astringents: Agents that exert a protective action on skin by precipitating proteins in superficial layers.
13. Demulcents: Agents that sooth the irritated skin or mucosa by preventing its contact with irritants.

## 4. Administration of Drugs

For a drug to act and produce its characteristic systemic effects, it must first be absorbed and then attain an effective concentration at its site of action. Most drugs can be administered by a variety of routes. The choice of appropriate route depends both on the drug as well as the patient related factors.

**Factors Governing the Choice of Route of Drug Adminstration**:

1. Physico-chemical properties of the drug
2. Site of desired action of drug: Localized or generalized.
3. Rate and extent of absorption of the drug from different routes.
4. Effect of digestive juices, ruminal microflora and first pass metabolism on the drug.
5. Rapidity with which the response is desired (routine treatment/emergency)
6. Intensity of action desired.
7. Type of response desired.
8. Accuracy of dosage required.
9. Condition of the patient (unconscious, vomiting, etc).

The routes of drug administration are: a) Local and b) Systemic.

**Local routes:**

These routes can only be used for localized lesions at accessible sites. Systemic absorption of the drug from these routes is minimal or absent. Thus, high concentrations are attained at the desired site without exposing the rest of the body. Systemic side effects or toxicity are absent or minimal. Topical application refers to local route of drug administration. The commonly used local routes include:

**Topical Application**: This refers to external application of the drug to the surface for localized action.

a) Skin: Drug is applied as ointment, lotion, liniment, powder etc.
b) Mucous membranes (Washing/cleaning of buccal mucosa; drug application as ointment/drops in eye, ear and nose; nonabsorbable drugs like aluminium hydroxide, kaolin, neomycin etc orally to act in GIT; ointment/suppositories intrarectally or intravaginally and placement of drugs in mammary gland (intramammary) or uterus (intrauterine) etc).

**Systemic routes:**

The drug administered through systemic routes is intended to be absorbed into the blood and distributed all over the body, including the site of action, through circulation. The different systemic routes of drug administration may be of two broad categories: Oral and Parenteral routes:

PO – (Per os dosing)

**Oral Adminstration**: Also termed enteral route (enteron meaning GI tract). It is one of the commonest, safer, noninvasive and painless methods. The medicament must not be sterile and so is cheaper route. A variety of dosage forms (solid, liquid, sustained release products) are administered orally. The route is also called 'PO' (per os dosing). Most drugs are absorbed better on empty stomach. Because of the extensive area and rich blood supply of its mucosal surface, the small intestine is the principal site of absorption for all drugs given orally. **Absorption of orally administered drugs is influenced by**:

* Absorption of orally administered drug is influenced by *.

a) Presence of food (complexing with ingesta/nutrients: retard absorption), pH of the environment.
b) pKa of the drug.
c) Effect of gut microflora (degradation)
d) Degradation in liver
e) Gastric emptying and
f) Changes in the intestinal blood flow.

Non-ionized lipid soluble drugs (ethanol) are readily absorbed from stomach (incuding rumen ) as well as intestine at rates proportional to their lipid:water partition coefficient. Most drugs are weak electrolytes and their ionization is pH dependent. Acidic drugs (aspirin) are largely unionized at acidic gastric pH and are absorbed from stomach, while bases (atropine) are largely ionized and are absorbed only when they reach the intestines Highly ionized drugs like streptomycin,neostigmine, are poorly absorbed when given orally.

**The limitations of oral route are**:

a) Action is slower and thus not suitable for emergencies.
b) Some drugs may cause nausea and vomiting.
c) Certain drugs are not absorbed (highly ionized) and
d) Destruction by digestive juices (Penicillin G, insulin) or in liver (testosterone).
e) Absorption of drug from GI tract may be slow, irregular and uncertain particularly in ruminants because of large volume of ruminal contents. Among monogastrics, the drug effects can be better predicted in carnivores than in herbivores.
f) In ruminants rumen fermentative activities and microbial population pose hazards for chemical stability of certain drugs (inactivation of chloramphenicol and digitalis glycosides).
g) Oral therapy with antimicrobials suppresses the beneficial effects of ruminal and intestinal microflora (Inhibition of vitamin synthesis and incidence of super infection).

**Parenteral Adminstration**: It is beyond enteron or GIT or away from GIT. This refers to administration mainly by injections which take the drug directly into blood or tissue fluid without having to cross the intestinal mucosa.

**Advantages**:

1. Absorbed more rapidly
2. Effective dose can be selected more accurately.
3. Action is faster and surer.
4. Interference by food and alimentary juices and first- pass metabolism are avoided and therefore the drug is absorbed in active form.
5. Economy of the dose is ensured.
6. Parenteral routes are preferable if the patient is unconscious or incooperative or already vomiting.
7. Gastric irritation and vomition are not provoked.

**Disadvantages**:

1. Strict asepsis and sterile condition should be maintained and, therefore expensive.
2. Relatively risky and there is chances of local tissue injury.
3. Invasive and painful (njections).

The parenteral route includes a) Injections, b) Inhalation, c) Transmucosal and d) Transcutaneous administration.

**a) Injections:**

Drugs are most commonly injected by intravenous (iv), intramuscular (im), subcutaneous (sc) and intraperitoneal (ip) routes with the help of a syringe and needle.

**Intravenous injection**: The drug is injected as a bolus (lump) or infused slowly over hours in one of the superficial veins.The drug directly reaches into the blood stream and effects are produced immediately (route of emergency). IV injections should always be performed slowly. except in special circumstances (Induction of anaesthesia by rapid iv injection of thiopental).The intima of veins are insensitive and drug gets diluted with blood. therefore, even highly irritant drugs and hypertonic solutions can be given only by the iv route.The dose of the drug required is smallest (bioavailability is 100%) and even large volume of the drug solutions can be infused. Only aqueous solutions (not suspension or in oily vehicle) can be injected iv. It is the most risky (dangerous) route of drug administration because vital organs like heart and brain get exposed to high concentrations of the drug. Therefore, great care must be taken in computing total dose and the speed of injection. There is chance of thromphlebitis of the injected vein, necrosis of adjoining tissues (if extravasation occurs). thrombosis or embolism.
In animals the common sites of iv injection are:

| | | |
|---|---|---|
| Jugular vein | : | Horse. cattle, sheep and goat |
| Dog | : | External saphenous/recurrent tarsal/ cephalic vein |
| Pig | : | Ear vein |

**Intramuscular injection:** The drug is injected in one of the large skeletal muscles (gluteal, rectus femoris and other thigh muscles in all species; neck muscles in pig horse and cattle). Muscle is less richly supplied with sensory nerves (a mild irritant may be injected) and is more vascular (absorption is faster). The peak plasma concentration occurs within 30 minutes. Depot/sustained release preparations, mostly of antimicrobial agents. are designed to give long duration of therapeutically effective plasma drug concentration [Procaine penicillin (aqueous suspension or in oil containing aluminium monosterate). oxytetracycline base in 2- pyrrolidone and protamine zinc insulin].

**Subcutaneous injection:** The drug is deposited in the loose subcutaneous tissue which is richly supplied by sensory nerves (irritant drugs cannot be injected). but is less vascular (absorption is slower). This route should be avoided in patients with CV shock (vasoconstriction: delayed absorption). Repository (depot) preparations lilke aqueous suspensions or oily solutions can be injected by this route for prolonged action. The sc injection site for horse and cattle is axillary fold and for dog is inner aspect of thigh.

**Intraperitoneal injection:** The drug is injected into the peritoneal cavity.This route is preferred in emergency administration of drugs as an alternative to iv route, especially in vicious and uncooperative animals or in very small animals or in cases of cutaneous burns. The ip route has importance in large animal practice for administration of large volume of nonirritant drug solutions because of its great absorbing surface and rapid absorption rate.

**Intradermal injection**: The drug is injected into the layers of skin. Only a small quantity of drug can be administered by this route and is primarly employed for diagnostic tests like tuberculin test. mallein test or many other allergic tests. Some vaccines are also injected intradermally (BCG and small pox in man).

**Intra-articular injection**: The drug is directly injected into the joint capsule (anti-inflammatory drugs).

**Intracardiac injection**: Injection of drug directly into the myocardium of the heart (adrenaline in sudden heart failure).

**Intramedullary injection**: Injection of drugs with a special type of puncture needle into the bone marrow of the sternum, femur and tibia. frequently employed in man and dog.

**Intraarterial injection**: Injection of drugs directly into the artery yields a transient but high concentration in the tissues supplied by the particular artery. This route is employed for injection of contrast media in angiography and for infusion of anticancerous drug in the femoral or brachial artery for limb malignancies.

**Intrathecal/ intraspinal injection**: Injection of drugs into the layer of meninges. It may be:
**Subarachnoid injection**: Drug is jectected into the subarachnoid space (lumbosacral) by lumbar puncture needle (Injection of antibiotics which cannot cross BBB in meningitis).
**Epidural injection**: Injection of drugs into the epidural space. Mainly employed for the purpose of regional anaesthesia using local anaesthetics, especially in large animals in place of general anaesthesia. Site is between 1st and 2nd coccygeal vertebrae in horse and cattle; between last lumbar and 1st sacral space in dogs.

**Inhalation**: Volatile liquid and gaseous anaesthetics are given by inhalation (ether, halothane, nitrous oxide etc). Rapid absorption takes place from large surface area of pulmonary alveoli ensuiring quick action. When administration is discontinued the drug diffuses back and is rapidly eliminated in expired air, ensuring controlled administration. Irritant vapours cause inflammation of respiratory tract and increase bronchial secretion. Pressurised aerosols, nebulised solutions or inhaler drugs like salbutamol are administered for trlief of bronchial asthma.

**Transmucosal**: It may be through sublingual, nasal and rectal mucosa.
**Sublingual**: Some drugs (as tablet or pellet) when placed under the tongue are dissolved and rapidly absorbed via sublingual mucosa. This route is sometimes employed in human medicine, but impracticable in veterinary medicine. Only lipid soluble and non-irritating drugs can be administered. The chief advantage is that liver is bypassed and drugs with high first-pass metabolism can be absorbed directly into the systemic circulation.The onset of action is rapid and once the desired effect is obtained the remaining drug can be discarded. Sublingually administered drugs in man are nitroglycerine (for coronary blood vessel dilatation) in angia, buprenorphine (analgesic) and nifedipine (antihypertensive).
**Nasal**: The mucous membrane of the nose can readily absorb many drugs bypassing the digestive juices and liver. This route is seldom used in veterinary medicine, but certain drugs as a spray or nebulized solution are used in man [1-deamino-8-D-arginine-vasopression, DDAVP or desmopressin (synthetic analogue of vasopression), GnRH and calcitonin].
**Rectal**: Certain mildly irritant and unpleasant drugs can be put into rectum as suppositories or retention enema for systemic effect particularly when the patient is having recurrent vomiting. Absorption is slower, irregular and unpredictable. Rectal inflammation can result from irritant drugs. Aminophylline, indomethacine, paraldehyde or diazepam sometimes given rectally in man.

**Transcutaneous**:
**Cutaneous**: Highly lipid soluble drugs can be applied over the skin for slow and prolonged absorption. The liver is bypassed. The drug is delivered into systemic circulation via the stratum corneum by diffusion (nitroglycerine, oestradiol, testosterone etc). This route is generally employed in man.
**Iontophoresis**: In this procedure galvanic current is used for bringing about the penetration of the drugs into deeper tissues where they may act upon the tissues in the neighbourhood of the point of application. Anode iontophoresis is used for compounds bearing a positive charges and cathode iontophoresis is used for the negatively charged compounds.The force of repulsion between similar charges drives the drug ion into the deeper tissues. Salicylates are used in this method in man.
**Inunction**: Certain drugs when rubbed into the skin (inunction) can get absorbed and produce their systemic effect (nitroglycerine ointment in angina pectoris in man).
**Jet injection**: This method involves the transcutaneous introduction of a drug by means of a high velocity jet produced through a microfine orifice, which does not require the use of a needle and is therefore painless. Insulin preparations for jet injection are available for use in diabetic human subjects.
**Replacement** refers to replenish the animal body by supply of hormones, vitamins, extra cellular fluids etc to correct the deficiency states. **Replacement therapy** aims at physiological level supplementation of deficient hormone or vitamin. Hormone supplementation/replacement therapy is usually adopted by subcutaneous implantation.

## EXERCISE

1. Describe the sources of drugs along with appropriate examples.
2. Give the classification of drugs basing on their source, describing in short about each source.
3. Describe the various active principles of herbal drugs along with examples.
4. What are common routes of drug administration in animals? Describe how absorption of an orally drug is altered.
5. Describe parenteral administration of drugs in animals.
6. What are injections? Describe common injection routes of drug administration in animals.
7. Describe what differences you observe while drug administration by oral and iv routes.
8. **Write a short note on the following:**
   a. Plants as drug sources
   b. Animals and microbes as drug sources
   c. Gene therapy
   d. Biopharmaceuticals
   e. Sites of injections in animals
   f. Parenteral drug administration
   g. Oral administration of drugs
   h. Oils
   i. Local administration of drugs
   j. Transcutaneous routes
   k. Transmucosal routes
9. **Differentiate between the following.**
   a. Alkaloid & Glycoside
   b. Resin & Oleoresin
   c. Oleoresin & balsam
   d. Volatile oil & Fixed oil
   e. Synthetic drug & Semisynthetic drug
   f. IV & IM injections
   g. IM & SC injections
   h. Local & Systemic administration
   i. Natural & Semisynthetic drugs
   j. Liquid paraffin & corn oil
   k. Glycone & Aglycone
   l. Saponin & Tannin
   m. Clove oil & Corn oil
   n. Catechu & Gumacacia
   o. Turpentine oil & Arachis oil
   p. Gene therapy & Drug therapy
   q. *In vivo* & *Ex vivo* gene delivery
   r. Injection & Infusion
   s. Inhalation & injection
   t. IV & IP injections
   u. Epidural & subarachnoid injections
10. **What do you mean by the following? Answer in one sentence for each.**
    a. Inhalation
    b. Infusion
    c. Topical application
    d. Local application
    e. Alkaloid
    f. Glycoside
    g. Tannins
    h. Saponins
    i. Mineral oil
    j. Fixed oil
    k. Intramammary administration
    l. Gene therapy
    m. Biopharmaceuticals
    n. Recombinant DNA technology
    o. Biotechnology
    p. Designer proteins
    q. Vectors
    r. *In vivo* gene delivery
    s. *Ex vivo* gene delivery
    t. Replacement therapy
    u. Iontophoresis
    v. Inunction
    w. Jet injection
11. **Give the most appropriate reason for the following statements in one or two sentences:**
    a. Gene therapy is not similar to conventional drug therapy
    b. Biopharmaceuticals are called designer proteins
    c. Gums can be used as suspending agents for drugs in liquid formulations
    d. Tannins exert astringent action on mucous membranes
    e. Tannins protect gastric mucosa against irritants
    f. Saponins may be considered as a subclass of glycosides
    g. Volatile oils are also called as aromatic oils
    h. Liquid paraffin is called as mineral oil
    i. Pathogenic microbes may also serve as therapeutic tools
    j. Oily solutions/suspensions are not to be injected iv
    k. SC implantation ensures sustained therapeutic effect
    l. Electrolyte/fluid therapy is done by slow iv infusion
    m. Inhalation of volatile drugs ensures very rapid absorption
12. **Matching:**
    a. Alkaloid : Atropine
    b. Tannin : Catechu
    c. Oleoresin : Tuepentine oil
    d. Resin : Jalap
    e. Aspirin : Synthetic drug
    f. Opium : Natural drug
    g. Shark liver oil : Vitamins A and D
    h. Glycoside : Digoxin
    i. Mineral oil : Liquid paraffin
    j. Corn oil : Fixed oil
    k. Clove oil : Volatile oil
    l. Sodium bicarbonate : Basic drug
    m. Aspirin : Acidic drug
    n. Gum : Acacia
    o. Inhalation : Vapours/Volatile drugs
    p. SC route : Systemic route
    q. Intramammary : Local administration
    r. Oily drug solution : IM injection
    s. Irritant drug solution : IV injection

# Chapter – 3 : PRINCIPLES OF DRUG ACTION: PHARMACOKINETICS

Pharmacokinetics is the study of processes of **absorption, distribution, metabolism** and **excretion** of drugs (how the body affects the drugs; movement or disposition of drug in the animal body). It quantifies the fate of a drug. by measurement of its concentration and metabolites in blood and urine over a period of time. after its administration.

A drug produces pharmacological or therapeutic effect when it reaches the site of action (from site of administration) in active form at a desired concentration. Pharmacokinetic data help us to determine the latency of or onset and duration of action, desired route, dose and frequency of administration of the drug enabling its proper clinical application or therapeutic use.

## 1. Drug Absorption

It is the processes by which the drug enters into blood circulation from the site of its administration. The concentration of a drug in plasma must be maintained for the desired therapeutic effect (therapeutic level). The recommended dosage schedule helps in achieving the therapeutic level of drugs. The range between the minimum and maximum effective therapeutic concentrations (achieved by minimum therapeutic dose and maximum allowable dose. respectivey) is called therapeutic window (area between minimum and maxium therapeutic doses of a drug). The drug concentration beyond the maxium effective level in plasma (due to administration of drugs above the maxiumum recommended dose i.e. overdosage) results in toxicity.

In the processes the drug has to pass through a series of cell membranes so as to enter the blood, tissues or target cells to exert it therapeutic effect. The processes by which drugs cross the cell membrane are mainly of two types: **Simple Transport** (Simple or passive diffusion and filtration) and **Specialized Transport** processes (Carrier mediated diffusion, Active Transport and pinocytosis).

**Simple Diffusion**: Drug molecules cross the cell membrane (CM) in the direction of concentration gradient (from high to low). Lipid soluble drugs diffuse by dissolving in lipoidal moiety of CM. It is directly related to: a) **Lipid: Water partition coefficient** of the drug. More the solubility in lipids. faster and more is the diffusion and b) **Ionization** of the drug and pH of the medium. Following oral administration weekly acidic drugs (aspirin or other salicylates and barbiturates) remain unionized in acidic gastric medium (pH 5) and hence are rapidly absorbed from stomach. In gastric mucosal cell such drugs are ionized (pH 7) and hence slowly cross the mucosal CM (**ion trapping**) and enter into the extra cellular fluid weakly basic drugs (atropine. ephedrine. morphine and quinine) get ionized and are not absorbed in stomach (acidity). They are nonionized in alkaline medium of the intestines and hence they are absorbed in the intestines. Nonelectrolytes (alcohol) are not ionized. their absorption is pH independent and hence are absorbed very rapidly from stomach or intestines.

**Filtration**: Lipid insoluble drugs cross the CM by filtration through the aqueous pores in the CM, if their molecular size is lesser than the diameter of the pores. Intestinal mucosa and RBC have very narrow pores (4 Å) and drugs with molecular weight more than 100 to 200 are not filtered. Capillaries (except in brain) have large pores (40 Å) and most drugs are filtered through these pores. This process is not related to lipid solubility or pH of the medium.

**Active Transport:** It occurs against the concentration gradient (lower to high). requiring a pushing force i.e. metabolic energy. The process involves a carrier system. The drug combines with the carrier leading to formation of drug-carrier complex which shuttles across the CM and translocates the drug molecule from one face of the membrane to the other. The drug-carrier system is specific (highly selective for the drugs). Same carrier can transport structurally similar drugs. The carrier system is subject to saturation (at high concentration of the drug). Active transport involves absorption of lipid insoluble drugs from GIT and renal or biliary secretion of drugs or their metabolites.

**Carrier-Mediated Diffusion or Facilitated Diffusion**: It is also in the direction of concentration gradient and does not require energy input similar to simple diffusion. Like active transport this process is also mediated/facilitated through a carrier system.

**Pinocytosis**: It is engulfment of macromolecules (large in size), similar to phagocytosis or feeding by amoeba. The CM invaginates to surround the macromolecule and then engulfs it into the cell (absorption of oral polio drops/vaccine or large protein molecules).

Simple/passive or facilitated diffusion, filtration and pinocytosis do not need energy.

**Factors Influencing Drug Absorption:**

1. **Water solubility**: Drugs in water solutions are rapidly absorbed than in solid form (disintegration and solubility) or in oily solutions.
2. **Concentration**: Higher the concentration at the site, rapid will be the absorption.
3. **Area of absorption**: Larger the area faster the absorption.
4. **Vascularity of the absorbing surface/area**: Increased blood flow/vascularity hastens drug absorption.
5. **Route of administration**: I/V instant (direct into blood). IM > IP > SC > Oral (po). After oral administration the drug absorption is delayed due to mixing or dilution of the drug by the ingesta (food material) or some drugs get inactivated (tetracycline by Ca in milk, protein drugs (insulin) by peptidases).

**Bioavailability:** It is a measure of the fraction of administered dose of a drug that reaches systemic circulation in the unchanged form. It gives the extent of absorption of drug in a dosage form as determined by its concentration-time curve in blood or by its excretion in urine. Bioavailability is low after oral administration (incomplete absorption or due to first pass metabolism or excretion in bile/feces). Incomplete bioavailability by parenteral route (IM, SC or IP) is less frequent, but may occur due to local binding of the drug at the site of injection. Bioavailability of IV injected drug is 100%.

## 2. Distribution of Drugs

After entering the systemic circulation (absorption) a drug gets distributed into interstitial and intracellular fluids (tissues). The apparent volume of distribution ($V_d$: Measure of drug distribution) may be defined as the volume of body fluid that would accommodate the entire drug if its concentration throughout the body was the same as in plasma. It reflects the amount of a drug present in the body as a multiple of that present in a unit volume of plasma.

Apparent volume of distribution ($V_d$) = Dose administered (IV) ÷ Plasma concentration

If the total amount of drug administered (IV) = 2000 mg, plasma concentration = 100 mg/L

$V_d$ = 2000 mg/100 = 20 L

The extent of drug distribution depends upon:

a) lipid solubility of the drug
b) Ionization of the drug at physiological pH
c) Extent of binding of drug to plasma and tissue proteins and
d) Differences in regional/tissue blood flow.

Movement of drug proceeds until equilibrium is established between unbound drug in plasma or tissues. Subsequently, there results a parallel decline in both the levels due to metabolism and excretion.

**Plasma Protein Binding:** In blood, drugs are bound to plasma protein (bound drug: inactive): Acidic drugs bind with albumin and basic drugs to $\alpha_1$ acid glycoprotein. The unbound form is called free drug (active). Protein binding is reversible and there exists equilibrium between bound and free forms of a drug. The free form is distributed in the interstitial and intracellular fluids, where it may also exist as bound and free forms. The active free drug is subject to metabolism and elimination. Thus over a period of time the amount of drug declines in the body, causing termination of its effects.

**Clinical Significance of Plasma Protein Binding of Drugs:-**

a) Highly plasma protein bound drugs are restricted to vascular compartment only
b) Plasma protein binding amounts to temporary storage of the drug.
c) Highly protein bound drugs are long acting (Phenylbutazone, warfarin, clofibrate etc)
d) Drugs having high affinity for plasma protein binding displace the drugs having low affinity to protein binding, resulting in sudden increase in effects of the latter drug (phenylbutazone and salicylates displace tolbutamide; indomethacin, ethacrynic acid and phenylbutazone displace warfarin; salicylates displace methotrexate) Acidic drugs do not displace basic drugs and *vice versa.*
e) Disease states alter plasma protein binding of drugs (reduced in hypoalbuminemia, and uremia and increased binding in pregnancy and inflammatory conditions: increase in $\alpha_1$-acid glycoprotein)

**Redistribution of Drugs**: It is a factor in terminating drug effects primarily when a highly lipid soluble drug that acts on brain, heart or kidney (high blood flow) is administered rapidly by iv injection or inhalation. Initially its concentration is high in these organs, but later it is taken up by less vascular bulky tissues (fatty tissues, skeletal muscles) resulting in decline in plasma concentration and termination of drug action (IV injection of thiopentone: immediate effect, but short duration).

**Tissue Storage of Drugs:-** Drugs may also accumulate in specific organs by binding to specific tissues structures (sequestration). The examples are:

| | | |
|---|---|---|
| Digoxin and emetine | : | In skeletal muscle and heart |
| Digoxin, emetine, chloroquine and tetracyclnes | : | In liver |
| Iodine | : | Thyroid |
| Chloroquine | : | Retina |
| Tetracyclines and heavy metals | : | Bone and teeth |
| Thiopentone, DDT, ether, phenoxybenzamine and minocycline | : | Adipose tissue |
| Chlorpromazine | : | Brain |
| Calcium | : | Collagen |
| Arsenic | : | Keratin |

Grieseofulvin is stored in skin, nails and hair roots.

**Blood Brain Barrier**: It is a physiological barrier protecting the vital centers of the CNS against the exogenously administered drugs. The capillary endothelial cells in brain have very tight junctions with very narrow intercellular pores and a neuronal layer covers the capillaries. These special anatomical features together called as blood brain barrier. Similarly the capillaries of choroid plexus also have tight endothelial junctions, serving the purpose of blood: CSF barrier. Both barriers are lipoidal and check the entry of nonlipid soluble drugs (streptomycin, neostigmine, hexamethonium etc: polar drugs), but permit only the lipid soluble drugs like anaesthetics and narcotics which exert effect on the CNS.

The capillaries and their endothelial cells also have several enzymes like monamine oxidase, acetyl cholinesterase, amidases etc which do not allow entry of active catecholamines, 5-hydroxytryptamine, acetyl choline etc into brain: Called **enzymatic blood brain barrier.**

**Passage of drugs through placenta**: Placental membranes are lipoidal and hence allow free passage of lipid soluble drugs into the fetal circulation. Lipid insoluble drugs if present in high concentration in maternal circulation also gain access into fetus. So, placenta serves as an incomplete barrier between maternal and fetal circulation.

## 3. Metabolism of Drugs (Biotransformation)

It is the process by which drugs undergo chemical alteration through reactions mediated by enzymes in the animal body. Liver is the principal site of metabolism of xenobiotics. The less important tissues capable of metabolizing drugs are intestine, lungs, kidney and plasma. Drug metabolism leads to (Functions/Purposes/Significance of Metabolism):

What is meant by metabolite ?

1. Conversion of an active drug to inactive metabolite (s): Most common reaction.
   Phenobarbitone to para hydroxy phenobarbitone
   Chloramphenicol to chloramphenicol-glucuronide
2. Conversion of a less active drug to a more active drug:
   Malathion/Parathion to Malaoxon/Paraoxon; Phenacetin to paracetamol; Phenylbutazone to oxyphenbutazone; Chloralhydrate to trichlorethanol
3. Conversion of an inactive drug (Prodrug) to an active drug/metabolite (Bioactivation):
   Prednisone to prednisolone: Bcampicillin to ampicillin; Levodopa to dopamine
4. Conversion of an active drug to an active metabolite of activity similar to the parent drug:
   Digitoxin to digoxin (both are cardiotonics): Dictrotophos to monocrotophos (both are insecticides)
5. Conversion of an active drug/compound to another active compound with different action
   Iproniazid (Antidepressant) to Isoniazid (AntiTB drug): Aflatoxin B1 (hepatotoxic) to Aflatoxin M1 (carcinogenic)

The active metabolites are further metabolized and in general the end products of biotransformation are eliminated from the body through excretion.

The reactions of drug metabolism are two types: I. Nonsynthetic (Phase I) and II. Synthetic (Phase II) reactions. A drug is metabolised by first phase reactions and then the metabolite (or metabolites) is (are) excreted directly or after conjugation through second phase reactions (aspirin is metabolized to salicylic acid and then as glucuronide conjugate).

**Nonsynthetic Reactions (Phase I)**: These include:
**Oxidation**: It is the most important drug metabolizing reaction and involves addition of oxygen/negatively charged radical or removal of hydrogen/positively charged radical. The examples of oxidative reactions are

a) N-dealkylation: Imipramine, diazepam, codeine, morphine, theophylline
b) O-delakylation: Codeine, indomethacin
c) Aliphatic hydroxylation: Ibuprofen, pentobarbital, meprobomate
d) Aromatic hydroxylation: Phenobarbital, phenylbutazone, acetanilid to paracetamol
e) N-oxidation: Quinidine, guanethidine
f) S-oxidation: Cimetidine, chlorpromazine
g) Deamination: Diazepam, Amphetamine to phenyl acetone
h) Dehalogenation: Chloroform to Phosgene
i) Desulphuration: Malathion to malaoxn

The oxidative reactions are catalyzed by a group of monoxygenases in liver (mainly present in microsomes) which in the final set up involve cytochrome-P-450 (haemoprotein), NADPH, cytochrome P-450 reductase and oxygen (Cyto P-450- Oxidation-reduction cycle). These enzymes are also called as microsomal oxidases or mixed functions oxidases.

**Reduction:** Reduction is acceptance of one or more electrons by the drug molecule from another metabolite or removal of oxygen/negatively charged radical or addition of hydrogen/positively charged radical. These reactions are mediated by hepatic microsomal nonmicrosomal enzymes called reductases. Through reduction amino or hydroxyl groups are formed in the drug metabolite. The reduction reactions are opposite to oxidation reactions. Some examples of reduction reactions are:

a) Nitroreduction: Active to inactive: Chloramphenicol.
b) Azoreduction: Inactive to active: Prontosil (to sulfonamide).
c) Carbonyl reduction: Inactive to active: Chloralhydrate to trichloroethanol: Active to inactive (Halothane).

The enzymes present in cytosol of liver and other organs and bacteria in intestines/rumen also catalyse reduction reactions:

a) Aldehyde reductase in hepatic cytosol: Chloral hydrate to trichloreathanol (inactive to active)
b) By rumen microflora: Nitrate to nitrite (inactive to active), Parathion to aminoparathion (active to inactive).

**Hydrolysis:** It is cleavage of drug molecules in the presence of water. The drugs which undergo hydrolysis are choline esters, procaine, lidocaine, pethidine etc. The enzymes involved are esterases, amdiases, epoxide hydrolase, proteases and peptidases

$$\text{Ester} + \text{Water} \xrightarrow{\text{Esterases}} \text{Acid} + \text{Alcohol}$$

$$\text{Acetyl choline} \xrightarrow[\text{[Water]}]{\textit{AchE}} \text{Acetic acid} + \text{Choline : Active to inactive}$$

$$\text{Enalapril} \xrightarrow{\text{Hydrolase}} \text{Enalaprilat (Inactive to Active)}$$

The Phase I reactions generally result in loss of pharmacological activity, however there are many exceptions (see above: Functions of Metabolism).

**Synthetic Reactions (Phase II):** Involve conjugation of the parent drug or phase I metabolite with an endogenous substance to form a highly polar ionized water soluble compound, which is readily excreted in urine or bile. The various types of conjugation reactions are:

a) Glucuronide conjugation: Acetaminophen, salicylic acid, chloroform, morphine, diazepam etc (most important reaction)
b) Sulfate conjugation (sulfation): Acetaminophen, steroids, methyldopa
c) Conjugation with acetate (acetylation): Sulfonamide, isoniazid, dapsone
d) Conjugation with methyl group (methylation): Histamine to N-methyl histamine; noradrenaline to adrenaline.
e) Conjugation with amino acids (glycine and glutamic acid): 2,4-D to 2,4-D-glycine conjugate
f) Glutathione conjugation (formation of mercapturic acid): Naphthalene to 1-naphthyl mercapturic acid and inactivation of epoxide intermediates formed during metabolism of certain drugs.
g) Thiosulphate conjugation: Cyanide to thiocynate

Drug conjugates are pharmacologically inactive (exception: a glucuronide conjugate of morphine is more potent as an analgesic than morphine). As these reactions are biosynthetic require energy input. The conjugates excreted through bile into intestines are subject to enzymatic (intestinal microflora) cleavage resulting in release of the drug, which is again absorbed into the systemic circulation. This phenomenon is called enterohepatic recycling, and may be associated with a delayed elimination of the drug and prolongation of its effects.

**Sites of Drug Metabolism:** Mainly liver, to some extent in GIT, kidney, skin, lungs and plasma. Following oral administration, a significant portion of the drug may be inactivated in either intestines or liver before it reaches systemic circulation (presystemic or first pass metabolism), significantly limiting its concentration reaching systemic circulation (bioavailability of orally administered drugs). The examples of drugs which undergo first-pass metabolism include: In liver: aspirin, morphine, propranolol, nitrates, salbutamol, catecholamines, ioniazid, verapamil etc and by intestinal microflora: Clonazepam.

The drug metabolizing enzymes are in endoplasmic reticulum of hepatocytes (hepatic microsomes): Hepatic microsomal enzymes. These enzymes are located in the smooth endoplasmic reticulum mainly in liver, but also in kidney, intestinal mucosa and lungs (monoxygenases, cytochrome P450, glucuronyl transferase etc). They catalyse most of the oxidations, reductions, hydrolysis and glucuronide conjugation.

The nonmicrosomal enzymes are found in the cytoplasm and mitochondria of hepatocytes and other tissues including plasma (esterases, flavoprotein oxidases etc); catalyse some oxidations, reductions, most hydrolytic reactions and all conjugation reactions, except glucuronidation.

**Enzyme Induction**: Increase in synthesis (*de novo*) of drug metabolizing enzymes especially microsomal oxidase cytochrome P 450 following exposure to certain drugs or environmental pollutants. It leads to an enhanced rate of biotransformation and corresponding reduction in the availability of the parent drug. Sometimes, due to enzyme induction (microsomal oxidases) the toxicity of the parent compound is increased (parathion to paraxon). It may also tend to decrease the plasma half life of a drug. The examples of drugs that cause enzyme induction are glucocorticoids, phenobarbitone, phenylbutazone, phenytoin, caffeine, nicotine, ethanol (chronic intake), DDT, carbamazepine etc.
**Enzyme Inhibition**: Some drugs also inhibit the synthesis of microsomal drug metabolizing enzymes, which include cimetidine, ketoconazole, quinidine, disulfiram (antabuse in alcoholism: Ethyl alcohol is metabolized to acetaldehyde by alcohol dehydrogenase and acetaldehyde is further metabolized by acetaldehyde dehydrogenase. Disulfiram inhibits acetaldehyde dehydrogenase, resulting in accumulation of acetaldehyde causing acute discomfort (acetaldehyde syndrome) characterized by nausea, vomiting, sweating, thirst, blurred vision, vertigo, headache, dyspnoea, vasodilatation and hypotension).

**Factors Altering Drug Metabolism**:

a) Metabolic drug interactions: Enzyme induction and inhibition by drugs and environmental pollutants.
b) Age: Very young or infants and old have reduced functional capacity of liver than adults.
c) Disease: Reduced in hepatic dysfunction (less blood flow or diseases)
d) Gender: Reduced activity of some enzymes in females (oxidation of oestrogens and benzodiazepenes).
e) Genetic Polymorphism: Genetical deficiency of drug metabolizing enzymes (cytochrome P 450 and its related enzymes and enzymes mediating N-acetylation) in individuals or a particular race or origin of people.

## 4. Drug Excretion

Drugs are eliminated from the body either in unchanged form or mainly as metabolites and conjugates. The metabolism renders the drugs more polar, less lipid soluble and more water soluble for ready excretion through kidney (urine) and/or bile (feces), the major routes of drug excretion.
**Renal Excretion**: Drug excretion through urine is dependent on **glomerular filtration** (which in turn is dependent on plasma protein binding, renal blood flow and GFR), **active tubular secretion** (active carrier mediated transport), **passive tubular diffusion** and **pH of the renal tubular fluid** i.e. urine (rapid excretion of acidic drugs in alkaline pH and rapid excretion of basic drugs in acid pH). About 20 % is excreted through glomerular filtration and the rest by other two processes.
**Biliary and Fecal Excretion**: Drug metabolites (glucuronides and steroids) formed in liver are secreted into intestines through bile and unabsorbed drugs following oral administration are excreted through feces. A portion of drug conjugates secreted through bile are hydrolyzed by intestinal microflora enzymes leading to liberation of free drug which is reabsorbed into circulation through **Enterohepatic cycling**. Lipid soluble drugs are reabsorbed via this cycle along with the bile. The enterohepatic recycling tends to create a reservoir of recirculating drug (about 20% of the total drug in the body) and helps in prolonging the action of such drugs. This process of enterohepatic recycling occurs repeatedly and ultimately the drug metabolites are excreted through urine. Pencillins, tetracyclines and erythromycin are excreted through bile. The minor routes of excretion of drugs or drug metabolites (insignificant) are through sweat, saliva, tears, milk, and lungs (significant for anaesthetic vapours and gases). Drugs or metabolites in milk may affect the nursing offspring. The presence of heavy metals like arsenic in hairs is of forensic importance.

**Drug Elimination:** It is the sum of metabolic inactivation and excretion of drugs. The ability of the body to eliminate a drug in a given period of time is measured by clearance.

**Drug Clearnce (CL)** is the theoretical volume of plasma from which the drug is completely removed in unit time and it is calculated as below:

**CL = Rate of Elimination / Drug Concentration in Plasma.**

If the rate of elimination of drug is 1000 microgram/ min and the drug concentration in plasma is 10 microgram per ml, the CL is 1000/10 = 100 ml per minute.

**Kinetics of Drug Elimination**: For most of the drugs, the elimination processes in clinical situations are not saturated and they follow first order kinetics of elimination (at therapeutic doses).

**First-Order (Exponential) Kinetics**: A constant fraction of the drug present in the body is eliminated per unit time, i.e. the rate of elimination is directly proportional to the drug concentration in the body. Hence CL remains constant.

However, a few drugs saturate the elimination process and thereby follow elimination kinetics called zero-order kinetics.

**Zero Order Kinetics**: A constant amount of drug is eliminated per unit time. Hence, the rate of elimination remaining constant and is independent of drug concentration, the CL decreases as the concentration increases. In this situation drugs are metabolized at a constant rate per time, as the enzymes involved become saturated. (alcohol, salicylates)

**Plasma half-life (t ½)**: It is the time taken for the concentration of a drug in plasma to get reduced half of its original concentration. Complete drug elimination occurs within 4-5 t½.

mixed kinetics & Absorption & rate of elimination problems

## EXERCISE

1. What is pharmacokinetics? What is the clinical significance of pharmacokinetic data of a drug? Discuss drug absorption following oral administration.
2. What is drug absorption? Describe the different drug absorption processes.
3. What is biotransformation of drugs? Discuss the functions of drug metabolism citing suitable examples.
4. Describe the different reactions of drug metabolism.
5. What is drug elimination? Describe the processes of drug excretion.
6. Discuss the different factors influencing drug absorption and metabolism.
7. **Write a short note on the following**:
   a. Specialized drug absorption processes
   b. Distribution and redistribution of drugs
   c. Plasma protein binding of drugs
   d. Functions/purposes of drug metabolism
   e. Synthetic reactions of drug metabolism
   f. Drug conjugation
   g. Phase I reactions of drug metabolism
   h. Drug metabolizing enzymes
   i. Enterohepatic cycle
   j. First-pass metabolism
   k. Presystemic drug metabolism
   l. Drug clearance
   m. Drug oxidation
   n. Drug reduction
   o. Drug hydrolysis
8. **What do you mean by the following? Answer in one or two sentences for each**:
   a. Drug absorption
   b. Drug biotransformation
   c. Drug distribution
   d. Drug elimination
   e. Biotransformation
   f. Drug oxidation
   g. Drug reduction
   h. Drug hydrolysis
   i. Drug conjugation
   j. Active transport
   k. Diffusion
   l. Filtration
   m. Facilitated diffusion
   n. Pinocytosis
   o. Ion trapping
   p. Blood-brain barrier
   q. Enzymatic-brain barrier
   r. Redistribution
   s. Filtration
   t. Bioavailability
   u. Glucuronidation
   v. Acetylation
   w. Enterohepatic cycle
   x. Drug sequestration
   y. First-pass metabolism
   z. Presystemic metabolism
   aa. Enzyme induction
   bb. Enzyme inhibition
   cc. Microsomal oxidases
   dd. Drug clearance
   ee. First order kinetics
   ff. Zero order kinetics
   gg. Volume of distribution ($V_d$)
   hh. Detoxication
   ii. Lethal synthesis
   jj. Bioavailability
   kk. t ½
   ll. Prodrug
   mm. Sulfation
   nn. Therapeutic window
   oo. Antabuse
   pp. Acetaldehyde syndrome

9. **Differentiate between the following**:
   a. Drug absorption & bioavailability
   b. Drug clearance and t ½
   c. Phase I & Phase II reactions
   d. Active transport & diffusion
   e. Diffusion & facilitated diffusion
   f. Microsomal & Nonmicrosomal enzymes
   g. Enzyme induction & inhibition
   h. Oxidation & reduction
   i. Drug & prodrug
   j. Bioavailability & t ½
   k. Distribution & redistribution
   l. Therapeutic level & Therapeuric window
10. **Substantiate the following statement by giving the most appropriate reason**:
   a. Drug effects in animals after oral administration are less pronounced
   b. Bioavailability of drug after oral dosing is incomplete
   c. Bioavailability after IM or SC injection is infrequently incomplete.
   d. Facilitated diffusion is sensitive to competitive inhibition
   e. Polar substances do not readily cross the cell membranes (are not absorbed)
   f. Acidic drugs are absorbed from stomach
   g. Basic drugs are not absorbed from stomach
   h. Acidic drugs are not absorbed in intestines
   i. Basic drugs are absorbed in intestines
   j. Toxic levels of heavy metals in body persist for longer periods
   k. Fatty animals require higher doses of an anaesthetic than the lean animals
   l. Drug effects persist for longer period in very young and very old animals
   m. Drug conjugates are readily excreted
   n. Active transport is called up the hill transport
   o. Diffusion is called down the hill transport
   p. Salicylates do not displace protein bound wafarin
   q. Pharmacokinetic data has value in clinical application of a drug
   r. Alcohol produces its effects rapidly after its oral ingestion
   s. Peptide drugs (insulin) are not be dosed orally
   t. Protein binding tends to serve the purpose of temporary storage of drugs
   u. Phenylbutazone intensifies the actions of warfarin
   v. Circulating drugs do not easily enter the brain
   w. Redistribution tends to terminate drug effects
   x. Enterohepatic cycle tends to prolong drug effects
   y. Through Phase II reactions drugs are inactivated (mostly)
   z. Urinary acidifiers enhance renal excretion of basic drugs
   aa. Urinary alkalizers enhance renal excretion of acidic drugs
   bb. Under first-order kinetics CL remains constant
   cc. Under zero-order kinetics CL decreases
   dd. In zero-order kinetics drugs are metabolized at a constant rate
   ee. In first-order kinetics a drug is eliminated as a constant percentage of its plasma concentration.
   ff. Enzyme induction decreases the plasma half-life of drugs.
   gg. Therapeutic window reflects the clinical efficacy of the drug.
9. **Give one example of the following reactions of drug biotransformation**:
   a. Oxidative inactivation
   b. Oxidative activation
   c. Reductive inactivation
   d. Reductive activation
   e. Hydrolytic inactivation
   f. Inactivation by microflora
   g. Activation by microflora
   h. Glucuronidation
   i. Acetylation
   j. Sulfatation
   k. Methylation
10. **Matching (Parallel pairs)/Multiple choices (Right choices):**
   a. Pharmacokinetics: Drug disposition in body
   b. Carrier mediated: Facilitated diffusion/Active transport
   c. Simple transport: Diffusion
   d. Specialized transport: Active transport/Facilitated transport
   e. Diffusion: Down the hill transport
   f. Active transport: Up the hill transport
   g. Acidic drugs: Absorbed in stomach
   h. Basic drugs: Absorbed in intestines
   i. Nonelectrolytes/Alcohol: Absorbed in stomach and intestines

j. Drug distribution: Lipid solubility/Ionization/Plasma protein binding/Blood flow
k. Acidic drugs: Albumin
l. Basic drugs: Alpha$_1$ acid glycoprotein
m. Thiopentone: Fatty tissues
n. Heavy metals: Bone and teeth
o. Aresinc: Keratin
p. Drug metabolism: Active to inactive/Inactive to active/Less active to more active/Active to active
q. Drug activation: Oxidation/Reduction/Hydrlysis
r. Microsomal enzymes: Monooxygenases/Cytochrome P450/Glucuronyl transferase/Oxidation/Reduction/Glucuronidation
s. Nonmicrosomal enzymes: Esterases/Flavoprotein oxidases/Oxidation/Reduction/Hydrolysis/Acetylation/Sulfation/Methylation/Glutathione conjugation
t. Microsomal enzyme induction: Glucocorticoids/Phenobarbitone/Phenylbutazone/Caffeine/Ethanol/DDT/Carbamazepine
u. Microsomal enzyme inhibition: Cimetidine/Ketoconazole/Quinidine/Disulfiram
v. Drug elimination: Drug metabolism/Drug excretion
w. Drug Cl: ml per min
x. First order kinetics: CL remains constant/Elimination is proportional to plasma concentration
y. Zero order kinetics: CL decreases/Elimination is independent of plasma concentration
z. Drug of hepatic first-pass metabolism: Catecholamines/Morphine/Verapamil/Isoniazid/Asprin
a. Drug of intestinal first-pass metabolism: Clonazepam

# Chapter – 4 : PRINCIPLES OF DRUG ACTION: PHARMACODYNAMICS

Pharmacodynamics deals with the study of how drugs act (mechanisms of action) in producing their effects (physiological and biochemical) and their intensity. Understanding of pharmacokinetics and phamacodynamics is the essence of modern pharmacology, and forms the pharmacological basis (scientific rationale) for judicious use of drugs in treating diseases.

## 1. Mechanism of Drug Action

It refers to study how drugs act and produce effects. It is also essential to understand how a drug produces its effects in altering the disease state to normal condition, which forms the pharmacological basis of therapeutics. Paul Ehrlich (in late 19th century) was the first to suggest that chemicals must bind to tissues in order to exert their effect while studying the antimicrobial action of arsenicals. Later J.N. Langely (in 1905) while investigating the action of curare on skeletal muscles substantiated the concept. It is now adequately explained that a great majority of drugs chemically interact with or bind to chemical groups of macromolecules the initial targets at cellular level in eliciting the pharmacological effects. The endogenous ligands (hormones, autacoids, cytokines, neurotransmitters or neuromodulators) and exogenous drugs induce patho-physiological and pharmacological effects through initial interaction with specific sub-cellular macromolecular sites of action. These are the sensory components of communication net work between the ligands/drugs and the cellular responses. The molecular interaction between the ligands/drugs (agonists) and sensory elements is translated and magnified in finally eliciting as cellular response (physiological, biochemical or pharmacological). There exists specificity between the agonists and the sensory elements. The composition and chemical structure of sites of initial reaction of many endogenus ligands/agonists are well understood and cloned for molecular pharmacology studies. The sensory elements or initial sites of drug interaction in cells are (targets of Drug Action) are of four types (all are protein in nature):

1. Receptors 2. Ion Channels 3. Enzymes and 4. Carriers/Transporters

**Receptors**: The concepts of drug binding to cellular components (later designated receptors), was put forwarded by Langely in the year 1878 while observing antagonism between pilocarpine and atropine. Susequently Paul Ehrlich (1905) substantiated Langely's corroborated concept of interaction between drug and the receptive substance and thus the drug-receptor interaction gradually gained acceptance. The quantitative generalizations of D-R interaction were explained by A.J. Clark (during 1933-1937)). He put forwarded the **theory of occupancy** in explaining the relation between D-R interaction and the effects which states that the response of a drug is proportional to the number receptors occupied by the drug. According to this theory there exists a complementary structural feature between drug and receptor similar to lock and key relationship where a drug exerts maximal response when it occupies all the receptors. Later Ariens (1957) modified the theory and stated that not only the occupancy of receptors the drug effect was also depended on the capacity (later referred as intrinsic activity) of the drug in producing a definitive response. Thus the concept of drug-receptor interaction: Involving affinity and intrinsic activity took roots. According to Arien's modification of occupancy theory, a drug can produce maximal response by not occupying the maximum number of receptors, but it depended upon intrinsic activity (later called agonist) and antagonism of action of a drug by another drug (antagonist) by occupying the receptors (having only occupancy/affinity), without exhibiting intrinsic activity (efficacy). Thus, Arien first tried to differentiate between agonists amd antagonists. The **rate theory** of D-R interaction was suggested by Paton which related the response as a function of rate of association between the drug molecules and the receptors. Several other theories are also suggested in explaining the D-R interaction. **Induced fit theory** proposed conformational change in receptor in closely alligining its active site with the drug molecule for interaction. **Perturbation theory** was explained in differentiating the confirmational changes induced in the receptor by an agonist and its antagonist (see below). The **activation-aggregation theory** suggested activation of D-R complex by agonists (response), but not by antagonists (no response).

The ability of a drug in binding to its receptor is called **affinity**. The ability of a drug to activate the receptor in producing the effects is called **efficacy (intrinsic activity)**. The initial interaction of drug molecules with receptors is called **drug action**. The events (physiological, biochemical or pharmacological responses) that follow subsequent to drug action are called **drug effect**. Therefore, the observed/measurable responses following administration of a drug are the consequence of **Drug Action-Activation-Effect Sequence**.

$$\text{Drug (D)} + \text{Receptor (R)} \xrightarrow{\text{Affinity}} \text{DR} \xrightarrow{\text{Activation : Efficacy (intrinsic activity)}} \text{Responses (Biochem./Physiol./pharmacological effects)}$$

The endogenous ligands (hormones, cytokines, autacoids, neurotransmitters or neuromodulators) have both affinity as well as efficacy and are called agonists. Drugs having both affinity and efficacy are also called **agonists**. The agonists obey action-activation-effect sequence. The **antagonists** (competitive in true sense, see later) interact with the receptors like an agonist, but fail to activate the receptor and do not produce the effect unlike an agonist, in addition antagonists also have ability to oppose the effects of the agonist. The antagonists do not obey action-activation-effect sequence. A drug with similar or less affinity than an agonist and produces effect less than that of the agonist is called **partial agonist**. A partial agonist produces only sub-maximal effect irrespective of increasing its dose. A drug having affinity similar to an agonist, but producing the response opposite to that of the agonist is called **inverse agonist**. In some instances, a drug having affinity to more than one type of receptor, it acts as the agonist on one type and as antagonist on the other receptor type; such a drug is called **agonist-antagonist**.

Thus, an agonist (**full agonist**) produces maximal response, a partial agonist produces sub-maximal response, an antagonist produces no response, an inverse agonist produces opposite response and an agonist-antagonist produces mixed response. The differentiation between the above drug categories is summarized below along with suitable examples.

| Category | Example | Receptor | Affinity | Efficacy | Effect |
|---|---|---|---|---|---|
| Agonist | Ach | Nicotinic | +++++ | +++++ | Contraction |
| | GABA | GABA | +++++ | +++++ | Sedation |
| | Nicotine | Nicotinic | ++++ | ++++ | Contraction |
| | Diazepam | GABA | ++++ | ++++ | Sedation |
| | Morphine | μ, δ, κ | ++++ | ++++ | Analgesia |
| Antagonist | d-tubocurarine | Nicotinic | +++++ | Nil | Paralysis |
| | Picrotoxin | GABA | +++++ | Nil | Stimulation |
| Partial Agonist | Buprenorphine | μ | ++ | + | Analgesia |
| Inverse Agonist | β-carbolines | GABA | +++++ | ++++ | Arousal |
| Agonist-Antagonist | Pentazocine | κ, σ | ++++ | + | Dysphoria |
| | | μ, δ | ++++ | Nil | No analgesia (weak antagonist) |

The examples of different types of receptors (above) are:

Type I: Ligand-gated ion channel receptors: nAChR and $GABA_A$.
Type II: G-protein coupled receptors: mAChR and adrenergic receptors.
Type III: Kinase-linked receptors: Insulin, growth factors and cytokines.
Type IV: Nuclear receptors: Steroid/thyroid hormones, vit.D, antidiabetic and hypolipaemic drugs.

**Ligand-Gated Ion Channel Receptors (ionotropic receptors)**: These are located closely associated with ion channels in cell membrane and are the receptors for the fast-acting neurotransmitters. The transmitter released from presynaptic nerve terminal acts on postsynaptic receptors selectively

increasing ion permeability of postsynatic membrane causing either depolarization or hyperpolarization (see synaptic transmission). The ligand-gated ion channels incorporate a receptor and are opened when an agonist (ligand) occupies the receptor The operation of these ion channels is modulated (opening) directly through binding of an agonist to the channel protein, causing selective permeability of cations ($Na^+$ or $K^+$. and anions $Cl^-$). The examples include: Nicotinic ACh receptor and the receptors of GABA, glycine, glutamate and aspartate (fast-acting neurotransmitters). The effects are seen instantaneously (within milliseconds).

guanine — **G-Protein Coupled Receptors (GPCRs)**: These are also located in cell membrane. The cellular effects of interaction of agonist with these receptors are mediated through a G-protein (containing guanine nucleotide GTP) and participation of **second messengers**. There is a functional link between the receptor, G-protein and second messengers in producing the cellular effects. The G-protein has two components, one stimulatory and the other an inhibitory component (bidirectional) which are called as **$G_S$ and $G_I$** respectively. The targets of GPCRs are enzymes adenylate cyclase, phospholipase C and phospholipase A which help in formation of second messengers cAMP, inositoltriphosphate ($IP_3$)/ diacetyl glycerol (DAG) and arachidonic acid, respectively and produce effects at cellular level through **transduction mechanisms** (the mechanisms of translation of receptor/enzyme activation into functional response in the cell). The effects of these receptors appear within a few seconds. These receptors are called metabotropic receptors.

G protein & ion channels.

Some G-protein coupled receptors are also linked to ion channels in the cell membrane, whose activation also produce cellular effects directly without the involvement of second messengers. The effects of direct action appear fast within a second. The examples are muscarinc Ach receptors in heart decreasing heart rate, opioid receptors in neurons causing analgesia (increase K ion permeability causing hyperpolarization-inhibition).

Catalytic domain. Ligand B. domain

**Kinase-Linked Receptors**: These are membrane bound receptors linked to a kinase having tyrosine residues. The actions of hormones like insulin, several growth factors and cytokines are mediated through these receptors. These receptors have an extracellular ligand binding domain and an intracellular catalytic domain. Agonist binding to the ligand domain activates tyrosine kinase or guanylate cyclase (formation of second messenger cGMP) and triggers a series of transduction mechanisms causing cellular effects. The effects that follow agonist binding to these receptors take hours to appear.

**Second Messengers and Transduction Mechanisms:**

**Adenyl Cyclase-cAMP System:** Activation of adenyl cyclase triggers formation of cAMP, which in turn activates a protein kinase which through phosphorylation reactions activates/inactivates other enzymes causing cellular effects. The transduction mechanisms in causing hyperglycaemia by adrenaline are explained as follows:

When the released epinephrine (from adrenal medulla) reacts with adrenoceptors ($\alpha_1$, $\beta_2$ and $\beta_3$; all G-protein coupled receptors) the stimulatory component of the receptor ($G_S$) is activated which stimulates the enzyme adenylate cyclase (AC). This enzyme in turn helps in formation of cAMP (second messenger) from ATP. The cAMP in turn activates an inactive protein kinase. The active protein kinase in turn activates the inactive lipase and phosphorylase kinase and inactivates glycogen synthetase, which mediate subsequent metabolic functions resulting in increased lipolysis and glycogen breakdown and reduced glycogen synthesis respectively.

cAMP = Cyclic

Activation of adenyl cyclase through stimulation of beta-adrenoceptors, $H_2$ and $D_1$ receptors. Inhibiton of adenyl cyclase is through $M_2$, alpha $_2$, $D_2$, mu and delta, $A_1$ and $GABA_B$ receptors.

 second messengers.

**Phospholipase C-Inositol Phosphate System:** Phosphatidylinositol Cycle (PI Cycle): Activation of membrane bound phospholipase C helps in formation of Inositol Triphosphate ($IP_3$) and Diacecylglycerol (DAG), both are second messengers, from cell membrane phospholipids phosphatidylinositol biphosphate ($PIP_2$). The $IP_3$ controls release of calcium ions from intracellular sites. The calcium ions bind to calmodulin, which in turn binds to several other proteins in the cell (kinases, phosphatases, transporters, transcription factors etc) causing cellular effects (excitation, contraction and secretion).
DAG activates a protein kinase C which catalyses phosphorylation of intracellular proteins and subsequent cellular effects.
**Tyrosine Kinase Activation:** Helps in phosphorylation of tyrosine residues in the cytosol. Phosphotyrosine residues bind to -SH domain of intracellular proteins (enzymes) causing cellular effects [cell growth/differentiation; gene transcription factors (which enter nucleus and cause protein synthesis)].
**Gunylate Cyclase-cGMP System:** Activation of guanylate cyclase helps in formation of cGMP (second messenger), which in turn activations a protein kinase G resulting in subsequent cellular effects.
**Phospholipase-Arachidonic Acid System:** Activation of phospholipase A2 helps in formation of arachidonic acid from the cell membrane phospholipids. Arachodonic acid serves as the precursor for formation of several eicosanoids which have a variety of cellular effects.

**Nuclear Receptors**: These receptors are located in cytoplasm and when a ligand is available in the cytosol migrate into nucleus where they control gene trancription. The ligands for these receptors are steroid and thyroid hormones, hypolipaemic and antidiabetic drugs and retinoic acid (embryonic development). The lipophilic drugs enter into the cell and then gain access into the nucleus. The steroids bind to the receptors resulting in formation of receptor dimers, which bind to the nuclear DNA. RNA polymerase activity is increased or decreased resulting in induction or inhibition of specific proteins/enzymes and the consequent cellular effects. The effects mediated through nuclear receptors are seen after several hours. The nuclear receptors regulate gene transcription and protein synthesis. A steroid drug binds to the nuclear receptor, which in turn binds to DNA, increasing RNA polymerase activity forming a specific mRNA resulting in synthesis of a specific enzyme (protein).

**Ion Channels**: The voltage-gated ion channels open when the cell membrane is depolarized, causing membrane excitability (through selective permeability of $Na^+$, $K^+$ or $Ca^{++}$) and cellular effects, or inhibited through physically blocking the of opening and permeability by inhibitors. The examples are:

1. **Excitatory Voltage-Gated Channels**:
   **Sodium Channels**: Increase in sodium ion permeability (Depolarization):
   Block Inactivation: Causing Persistent Depolarization (remain opened): Batrachotoxin, veratridine, scorpion toxins etc.
   Block Sodium Conductance (No depolarization): Tetrodotoxin, local anaesthetics, some antiepileptics, some antidysrrhythmic drugs etc.
   Sodium Channels are physically blocked by DDT.
   **Calcium Channels**: Increase calcium ion permeability:
   Activation: Histamine, angiotensin, Beta-adrenoceptor agonists (smooth muscles).
   Inhibited: Divalent cations ($Cd^{++}$)
   Blocking: Nefedipine, guanafacine, guanabenz etc.
2. **Inhibitory Voltage-Gated Channels**: Hyperpolarization : Increase K ion permeability
   Tetramethylammonium (TMA), dendrotoxins, many neurotransmitters.

**Enzymes**: The enzymes are located extracellularly or intracellularly. Drugs through action on enzymes produce effects in several ways:

**A. Inhibition of Enzymes:**

a. AChE by organic phosphate and carbamate insecticides, physostigmine and neostigmine.
b. Phosphorodiesterase by theophylline, caffeine, sildenafil etc.
c. Angiotensin-converting enzyme by captopril, enalapril etc.
d. Cyclooxigenases by aspirin and other NSAIDs.
e. Monamine oxidase by iproniazid and selegiline.
f. Viral thymidine kinase by acyclovir.
g. Bacterial transpeptidase by beta-lactam antibiotics.
h. Protozoal folic acid reductase by pyrimethamine.

**B. False Substrate-False Metabolite:**

a. Formation of alpha methyl Norepinephrine from alpha methyl DOPA.

**C. Formation of Active Drug/Metabolite from Prodrug:**

a. Dopamine from L-Dopa
b. Ampicillin from Bacampicillin

**Carriers**: The protein carrier molecules present in cell membrane serve the function of carrying/transpoting the ions, essential metabolites, neurotransmitters and small drug molecules into the cell. Several drugs through inhibition of carrier proteins and produce their effects. The examples include:

a. Choline entry into cholinergic nerves by hemicholinum
b. Norepinephrine uptake into adrenergic nerve terminals by tricyclic antidepressants and cocaine.
a. Norepinephrine uptake into synaptic vesicles in adrenergic nerve terminals by reserpine.
b. $Na^+$-$K^+$-2Cl- cotransport in loop of Henle by loop diuretics.
c. $Na^+/K^+$ ATPase (pump) by cardiac glycosides.

Several lipid insoluble metabolites (amino acids, glucose) or polar drugs do not diffuse across the cell membrane. Their entry into cell is mediated by carrier proteins.

**Receptor Specificity**: Receptors for a particular agonist or its analogues. One class of agonist does not interact with receptor of other class agonist (histamine with H receptors, but not with adrenoceptors; adrenaline with adrenoceptors, but not with H receptors, Ach with cholinergic receptors, but not with adrenoceptors or H receptors etc).

**Reserve** receptors or **spare** receptors are those receptors (**pharmacological** receptors) in excess of the receptors that are required for the maximal response of an agonist. **Silent** or **inert** receptors are those receptors where interaction or binding of a drug with such receptors does not elicit a pharmacological response (drug storage sites like plasma proteins).

**Receptor sites** (**active sites** of receptors) are the chemical groups of the receptors where there is actual contact or interaction of the drug molecule occurs (esteratic and anionic sites of AChE). The drug-receptor interaction involves binding forces such as ionic bonds, hydrogen bonds and Van der Waals forces.

There are many drugs, whose mechanism of action does not involve interaction with receptors as described above (**nonreceptor-mediated mechanism of action**); these drugs are diuretics, antacids and urinary acidifiers or alkalizers.

## 2. Pharmacometrics

It refers to measurement of drug responses on biological systems.

**Dose Response Relationship**

The relative potency of an unknown drug in comparison to a standard/known drug can be estimated by using dose responses curves. These curves are graded dose response curve and quantal dose response curve. These curves illustrate the response of unknown and standard drugs at equi-potent doses. The comparison in their dose response curves (parallel line assays) explains their relative potency. The intensity of response produced by a drug is the function of its dose administered. The relationship between dose and response is represented, measured and interpreted through dose response curves: Graded dose response and Quantal dose response curves.

**Graded Dose Response Relationship**: The intensity of response gradually increases with the increase in dose (up to a level), where the size of response to a drug is measured in a **single biological unit** (animal/tissue or organ). It shows that when the dose exceeds a critical level (**threshold dose**) the response also increases progressively until it reaches the maximum or ceiling level (steady level, ceiling effect). The threshold dose is the minimum dose required to produce a measurable response. The minimum dose producing the maximal or ceiling effect is **ceiling dose** and any further increase in dose above ceiling dose will not result in further increase in response.

**Quantal Dose Response Relationship**: It gives the proportion of subjects (qunatum or %) in a population responding or not responding to the effect of a drug: All or None / Yes or No dose-response relationship. As in graded dose response there is no gradation (intensity) of response in quantal dose response (QDR), but indicates only % responding or % not responding; % awake or % slept, % dead or % alive, % cured or % not cured etc. The graded response does not reflect individuals' variation as noted under QDR. The QDR curve is used to determine the effective, toxic, lethal or any other fixed response.

In case of graded dose-response relationship, when the magnitude of response is plotted against the arithmetic units of doses, a hyperbolic curve is obtained. However, when response is plotted against logarithmic doses, a sigmoid curve ("S" shaped) is obtained, where the central portion is almost linear. Log dose response curves (LDRC) help to know relative potency, efficacy and selectivity of different drugs.

The quantal LDRC is used to find out the median effective, toxic or lethal doses of different drugs in arriving at therapeutic efficacy from a simple ratio of median lethal dose ($LD_{50}$) and median effective dose ($ED_{50}$) : $LD_{50} \div ED_{50}$, called **therapeutic index (TI)**, higher the ratio safer the drug. Penicillin has very high TI and digitalis has low TI.

The **therapeutic ratio (TR)** is the ratio of $LD_{25}$ to $ED_{75}$ and it is expressed by $LD_{25} \div ED_{75}$. The TR gives a better index of safety of a drug, as it also includes steepness of the curve.

The margin of safety of a drug can be better expressed through **standard safety margin (SSM)** which is a ratio of extremes of the QDR such as $\mathbf{LD_1 \div ED_{99}}$ **or** $\mathbf{LD_{0.1} \div ED_{99.9}}$ (minimum toxic or lethal dose ÷ maximum effective dose). This factor indicates the aim of drug usage i.e. achieving therapeutic effect without causing toxicity among patients. Drug safety can also be determined by finding out its **certain safety factor (CSF)**, which is calculated by: $\mathbf{[(LD_1 \div ED_{99}) - 1]\ 100}$ or $\mathbf{[(LD_{0.1} \div ED_{99.9}) - 1]\ 100}$, Which shows that the dose effective in 99 out of 100 animals or 999 out of 1000 animals has to be raised by a certain percentage (factor) to be lethal to 1 out of 100 or 1000 animals.

## 3. Drug Potency

It refers to the dose of a drug required to produce a particular effect of given intensity. Potency and dose are inversely related. Higher the dose required, to produce a particular response, lower is the potency of that drug and *vice versa*. Potency is a relative term in comparing a particular response by

different drugs. (Example: SC injection doses of morphine and hydromorphine for analgesia in a dog are 0.2 and 2.0 mg/kg, respectively. Thus, hydromorphine has one-tenth the potency of morphine). The LDRCs of different drugs with decreasing potency shift to right and with increasing potency shift to left). The median doses $LD_{50}$ and $ED_{50}$ respectively indicate the toxic and curative potency of drugs. By comparing the median doses of different drugs they can be classified as less potent, more potent, most potent or less toxic, more toxic, most toxic and so on.

**Latency or Latent period** is the time interval between termination of administration of drug and time at which its concentration in plasma is high eough to produce the effects. The latency varies depending upon route of administration, it is shortest by iv injection, followed by im, ip and sc injections and longest after oral administration.

**Duration of action (DOA)** is the period or time course during which a drug will continue to produce the desired therapeutic effect. It also varies according to route of administration of the drug. Following iv injection the DOA is short, since the drug is eliminated at a rapid rate. Following im or sc injections, the blood levels of a drug are at a steady level (slow rates of absorption and elimination) causing longer DOA as compared to iv or ip injection. Slow releasing or sustained drug formulations meant for im injection or sc implantation prodce prlonged or extended DOA (sustained blood levels due to delayed absorption).

**Onset of drug action** is the interval between administration of the drug and appearance of first signs of drug action.

**Therapeutic effect** is the response of the cellular components of the host resulting in reversal of the disease state to normal condition. It may be due to direct or indirect action of the drug. The direct action is through receptors of the host cells, causing alteration of the prevailing (pathological) situation to normal or physiological status. The indirect action is through revomal, mitigation or suppression of the invading pathogen.

**Site or Target of drug action** is the actual location of the body (tissue/organ) where the drug is intended to alter the function by interacing with the cellular components (receptors, ion channels, enzymes or carrier proteins): Anaesthetics on CNS, analgesics on sensory nerve endings/pain pathways, intestinal astringents on intestinal mucosa, cardiac glycosides on heart, diuretics in renal tubles etc).

## 4. Drug Assay

It refers to quantitative estimation of an active drug component (in a drug preparation) in order to determine its potency in comparison to a standard or pure drug. It is of three types: Chemical assay, bioassay and immunoassay.

**Chemical assay**: It consists of determination of concentration of the drug by chemical methods (spectrophotometry, fluorometry, GLC, HPLC or mass spectroscopy). This is the most common method of drug assay (salicylates, analgesics, sulfonamides, phenothiazine derivatives, biogenic amines etc).

**Bioassay**: Refers to estimation of quantity of a biologically active agent in a unit quantity of the drug preparation (test drug) in comparison to the response produced by the standard or reference drug. Bioassay is laborious, time consuming, expensive and in some instances less accurate as compared to chemical assay. Bioassay is recommended when other sensitive or reliable methods are not available as under the following circumstances:

a) When the chemical nature of the test drug is not known.
b) When the chemical nature of the drug is known, but it cannot be easily isolated or purified, may due to decomposition.

c) When the drugs having same pharmacological action, but different chemical structure exist together.
d) When the drug exists as isomers with different biological activities.

Bioassay procedures utilize the response of the whole animal, an isolated tissue preparation or microorganisms for comparison of responses between the unknown (test drug) and the standard drug. The whole animal techniques include assay of NorA on spinal cat BP, digitalis glycosides in causing cardiac arrest in guinea pig or frog, insulin by hypoglycaemic convulsions in mice, d-tubocurarine or muscle relaxants in causing head drop in rabbits etc. Isolated tissue preparations are used for assay of Ach (contraction of frog rectus abdominus muscle or leech dorsal muscle), histamine (contraction of guinea pig ileum), adrenaline (relaxation dioestrus rat uterus), 5-HT (contraction of rat fundus strip or dioestrus rat uterus), oxytocin (oestrus rat uterus), antibiotics (zone of inhibition against bacteria) etc.

**Immunoassay**: Generally used for assay of hormonal preparations. The assay depends upon reaction between a hormonal antigen and its specific antibody. The antibodies are obtained from sera of animals after repeated injection of pure hormone (antigen). The competitive inhibition of binding of radiolabelled hormone to the antibodies by unlabelled hormone, where the proportion of labeled hormone (or bound/free ratio) decreases as the concentration of unlabelled hormone increases. A standard graph is plotted using bound/free ratios of labeled hormone against standard concentration of unlabelled hormone. Under the same conditions, the test material (plasma) containing an unknown concentration of unlabelled hormone is allowed to react with the mixture of known concentration of labeled hormone and antibody. The bound/free ratio so obtained with the unlabelled test sample (plasma) is read on the standard graph to arrive at the concentration of the hormone in the test fluid. Radioimmunoassay is the most sensitive method of estimation of minute quantities of biologically active agents like hormones.

## 5. Combined Action of Drugs

When two or more drugs are given simultaneously or in quick succession, the response of one drug is altered by the other drug (**drug interaction**) as reflected by **decrease or increase** in the observable response due to interaction at pharmacokinetic or pharmacodynamic level.

**Pharmacological terms related to increase in response:**

**Synergism**: It is pharmacological cooperation (Greek words Syn and Ergon meaning work together) between two drugs, one facilitating or increasing the action of the other. It can be additive or supraadditive.

**Additive**: The pharmacological effect of the two drugs in combination is sum of the pharmacological effects of the two drugs when given individually (Drug A effect = ** and Drug B effect = **; Effect of Drugs A + B = ****). It is simply **summation** (2+2 =4). Examples: Aspirin + paraacetamol as antipyretic and analgesic; ephedrine + theophylline as bronchodilator; sulfadiazine + sulfamethazine as antibacterial etc. Here the drugs share a common mode of action generally.

**Supraadditive**: Usually referred as potentiation. The pharmacological effect of the drugs in combination is more than the simple summation of their individual effects (2 + 2 = 6). The drugs do not share the common mode of action. Examples: Potentiation of sulfonamides by trimethoprim; potentiation of local anaesthetics by adrenaline or hyaluronidase; potentiation of insecticidal activity of pyrethrins by piperonyl butoxide, pyrimethamine and sulfadiazine in treatment of chloroquin resistant *P. falciparum* malaria etc.

**Pharmacological terms related to decrease in response:**

**Antagonism**: It refers to decrease in or preventing or reversal of the pharmacological response of one drug by another drug. An antagonist is a drug antagonizing the action or effects of an agonist. Antagonism is of several types:

**Pharmacological Antagonism:** It is receptor antagonism and may be of two types:

**a. Competitive Antagonism**: The antagonist is structurally similar (analogous) to the agonist and hence prevents the access of the latter to its receptors and itself occupies the receptors (both act on same receptor). Antagonist reduces the affinity of agonist. Increasing the concentration of agonist can reverse the antagonism. The LDRC of agonist in the presence of competitive antagonist shifts to right. This is also called as reversible or surmountable or antagonism. Examples: Acetylcholine (agonist) and atropine (antagonist); morphine (agonist) and naltrexone (antagonist) etc.

**b. Noncompetitive Antagonism**: The antagonist is not chemically related to the agonist and may not act on the same receptors. Antagonist irreversibly binds to the sites adjacent to the receptor and makes it unsuitable for interaction with agonist. Antagonist reduces the efficacy of the agonist. Increasing the concentration of agonist cannot reverse antagonism. The LDRC of an agonist in presence of antagonist is flattened. The antagonism is also called as irreversible or unsurmountable antagonism. Examples: Acetylcholine (agonist) and decamethonium (antagonist); diazepam (agonist) and bicuculline (antagonist) etc.

**Physiological or Functional Antagonism**: The drugs in combination exert pharmacological effects in opposite direction by acting on different receptors: Histamine (↓) and adrenaline (↑) on BP and bronchial smooth muscles (constriction and dilatation); glucagon ( ↑ ) and insulin (↓) on blood sugar.

**Physical Antagonism**: Physical inactivation of one drug by the other: Adsorption of alkaloids and prevention of their absorption by activated charcoal.

**Chemical Antagonism**: Chemical inactivation of one drug by the other: Oxidation of alkaloids by potassium permanganate, chelation of Hg, Pb, As by BAL or Ca by sodium EDTA.

**Dispositional Antagonism**: One drug alters absorption or enhances the excretion of other drug through preventing its absorption or augmenting its excretion: Acidification of urine increases renal clearance of basic drugs (amphetamine) or alkalization of urine increases excretion of acidic drugs (barbiturates or salicylates) and absorption of acidic and basic drugs as influenced by pH in stomach and intestines.

## 6. Structure Activity Relationship

Drugs produce pharmacological effects by interacting with chemical groups of receptors. Thus the drug-receptor interaction and subsequent responses are dependent on the chemical structure of the drugs. Chemical structure determines the effects and potency (action and efficacy) of drugs. Basing on chemical structure pharmacological effects can be anticipated. Drug effects vary as the chemical structure is altered. Examples are:

a) **Increase in duration of a particular effect**: Procaine (local anaesthetic) has transient cardiac depression, but procainamide has marked cardiac depression.
b) **Decrease in duration of a particular effect**: Atropine on eye has persistent mydriasis and cycloplegia (5-7 days). but homatropine has both effects of shorter period (12-24 hr).
c) **Restriction of activity to a particular system**: Chlorpromazine has potent sedation and autonomic effects (antiadrenergic, anticholinergic and antihistaminic) with less antipsychotic effect, but trifluoperazine has potent antipsychotic effect with mild sedation and autonomic effects.
d) **Minimizing or removal of adverse/toxic reactions**: Use of nicotinic acid in pellagra causes flushing of skin and fall in BP, but use of nicotinamide is not associated with such adverse effects.

e) **Altered susceptibility to inactivation**: Penicillin G is inactivated by penicillinase, but its synthetic derivative oxacillin is resistant to penicillinase.

f) **Formation of competitive antagonists**: Paraaminobenzoic acid (PABA) is essential for bacterial growth, but paraaminosalicylic acid and sulfonamides competitively inhibit utilization of PABA by bacteria. Morphine is an analgesic, but nalorphine is its antagonist. Isoproterinol is a beta-adrenoceptor agonist, but dichloroisoproterinol is a beta-adrenoceptor antagonist.

g) **Change in site of action**: Pentamethonium is a competitive antagonist of acetyl choline at autonomic ganglia, but decamethonium is a noncompetitive antagonist of acetylcholine at neuromuscular junction.

h) **Variable agonistic function at receptors**: Adrenaline is an agonist of both alpha and beta adrenoceptors, phenylephrine is agonist of alpha receptors and isoproterinol is agonist of beta receptors.

## EXERCISE

1. What do you mean by pharmacological basis of therapeutics? Discuss the significance of pharmacokinetic and pharmacodynamic data in judicious use of drugs in treatment of diseases.
2. What are the initial targets of drug action? Explain drug-receptor interaction with theories.
3. What are receptors? Explain different receptor types.
4. What are ligands? Explain different types with suitable examples.
5. Name the second messengers and discuss transduction mechanisms in causing cellular effects.
6. Describe the mechanisms of drug action through G-protein-coupled receptors.
7. What are ion channels and their types? Describe the mechanisms of drug action through ion channel receptors.
8. Describe mechanisms of drug actions through enzymes and carrier proteins.
9. What is pharmacometrics? Describe how you record dose-response relationship.
10. What are dose-response curves? Describe with appropriate illustrations.
11. What is drug assay? Describe different methods of drug assay with merits and demerits of each.
12. What is drug potency? Discuss how quantal dose-response study help in determining drug potency.
13. Describe the joint actions of drugs with suitable examples.
14. What is drug antagonism? Describe different types of antagonism with suitable examples.
15. What is SAR? Describe its significance with suitable examples.
16. **Write short notes on the following**:
    a. Receptor types
    b. Theories of drug-receptor interaction
    c. Ion channels
    d. G-protein-coupled receptors
    e. Second messengers
    f. Adenyl cyclase-cAMP system
    g. Phosphorylase-Inositol Phosphate system
    h. Transduction mechanisms
    i. Nuclear receptors
    j. Graded dose-respone curve
    k. Quantal dose-response curve
    l. Drug potency
    m. Drug assay
    n. Bioassay
    o. Synergism
    p. Summation
    q. Potentiation
    r. Antagonism
    s. SAR
    t. Clarks's theory
    u. Median doses
    v. Inotropic receptors
    w. Metabotropic receptors
    x. Drug action-activation-effect sequence
17. **Differentiate between the following**:
    a. Drug action & Drug effect
    b. Affinity & Efficacy
    c. Agonist & Antagonist
    d. Agonist & Partial agonist
    e. Agonist & Inverse agonist
    f. Ligand-gated channels & Voltage-gated channels
    g. Rate theory & Occupation theory
    h. Graded & Quantal dose-response curves
    i. $ED_{50}$ & $LD_{50}$
    j. Threshold and Ceiling doses
    k. Therapeutic index & Therapeutic ratio
    l. Log dose and Arithmetic doses
    m. Percentage & Probit
    n. Dose & Potency
    o. Bioassay & Chemical assay
    p. Additive & Supraadditive effects
    q. Summation & Potentiation
    r. Competitive & Noncompetitive antagonism
    s. $G_s$ & $G_i$
    t. Direct & Indirect Actions
    u. Latency & Onset of action
    v. Pharmacological & Silent receptors
    w. Reserve & Silent receptors
    x. Receptor & Functional antagonism
    y. Pharmacological & Functional antagonism

18. **What do you mean by the following**:
    a. Receptor
    b. Agonist
    c. Antagonist
    d. Inverse agonist
    e. Partial agonist
    f. Competitive antagonist
    g. Agonist-antagonist
    h. Affinity
    i. Efficacy
    j. Action
    k. Effect
    l. Intrinsic activity
    m. Ligand-gated channels
    n. Voltage-gated channels
    o. G-protein-coupled receptors
    p. Kinase receptors
    q. Inotropic receptors
    r. Metabotropic recptors
    s. Receptor sites
    t. Carriers
    u. Threshold dose
    v. Summation
    w. Potentiation
    x. Competitive antagonism
    y. Functional antagonism
    z. Physiological antagonism
    aa. Dispositional antagonism
    bb. Chemical antagonism
    cc. SAR
    dd. Latency
    ee. Potency
    ff. $LD_{50}$
    gg. $ED_{50}$
    hh. Therapeutic index
    ii. Therapeutic ratio
    jj. SSM
    kk. CSF
    ll. Graded response
    mm. Quantal response
    nn. Threshold dose
    oo. Ceiling dose
    pp. Bioassay
    qq. Receptor-Drug binding forces
    rr. Spare/Reserve receptors

19. **Indicate the pharmacological terminology for the following joint actions of drugs**:
    a. Antibacterial effect of penicillin and streptomycin combination : Summation
    b. Pyremethamine and sulfadiazine against chloroquin-resistant *P. falciparum* malaria: Potentiation
    c. Sulfonamide and trimethoprim antibacterial combination: Potentiation or Supraadditive effect
    d. Ephedrine and aminophylline on bronchial dilatation: Summation or additive effect
    e. Aspirin and paraacetamol as antipyretic combination: Summation
    f. Local anaesthetics with adrenaline- prolongation of local anaesthesia: Potentiation
    g. Insecticidal combination of pyrethroids and piperonyl butoxide: Potentiation
    h. Atropine against Ach: Competitive antagonism
    i. Phentolamine on adrenoceptors: Competitive antagonism (adrenoceptor blockade)
    j. Morphine and naltrexone: Competitive antagonism of morphine
    k. Decamethonium and Ach at motor end plate: Noncompetitive antagonism of ACh
    l. Papaverine and ACh on intestinal smooth muscles: Functional antagonism
    m. ACh or histamine and adrenaline on BP: Functional/physiological antagonism
    n. BAL against heavy metals or Disodium EDTA on calcium: Chemical antagonism
    o. Activated charcoal with alkaloids/metals/toxicants: Physical antagonism
    p. Enhanced renal excretion of barbiturates by urinary alkalizers: Dispositional antagonism
    q. Enhanced renal excretion of amphetamine by urinary acidifiers: Dispositional antagonism
    r. Combined effects of two drugs is equivalent to sum of their individual effects: Summation
    s. Combined effects of two drugs is equivalent to more than sum of their individual effects: Potentiation
    t. Insulin and glucagon on blood glucose levels: Functional/physiological antagonism

20. **Explain the following with appropriate illustrations**:
    a. Graded dose-response curve
    b. Quantal dose-response curve
    c. Log dose-response curve (LDRC)
    d. LDRCs of agonists with decreasing potency/affinity shift to right
    e. LDRCs of an agonist in competitive antagonism shift to right
    f. LDRCs of an agonist in noncompetitive antagonism tend to flatten
    g. Summation (Additive effect)
    h. Potentiation (Supraadditive effect)

21. **Substantiate each of the following pharmacological facts with the most suitable explanation in one or two sentences**:
    a. Langely is regarded as the originator drug-receptor interaction.
    b. Ariens and Stephenson extended the concepts of Clark.
    c. Agonists produce pharmacological effects.
    d. Antagonists fail to produce observable response.
    e. Competitive antagonists prevent the pharmacological effects of agonist.
    f. An agonist produces full response.
    g. A partial agonist produces submaximal effect.
    h. An agonist-antagonist produces mixed pharmacological responses.
    i. Interaction with the same receptor results in opposite effect.
    j. G-protein-coupled receptors (G-P-CRs) are called bidirectional receptors.
    k. cAMP, $IP_3$ or DAG is called a second messenger.
    l. Ligands can be designated as first messengers.
    m. Effects of steroid drugs/Vitamin D are delayed.

n. Steroid drugs cause enzyme induction.
o. Drug actions through nuclear receptors induce or inhibit protein synthesis.
p. Carriers are sensitive to competitive inhibition.
q. Dose and potency are inversely related.
r. Therapeutic index reflects drug safety.
s. In plotting dose response curves log doses are used instead of arithmetic doses.
t. LDRCs of an agonist in presence of competitive antagonist shift to right.
u. LDRCs of agonists with decreasing affinity/potency shift to right.
v. LDRCs of an agonist tend to flatten in presence of a noncompetitive antagonist.
w. Synergism is called pharmacological cooperation.
x. Supraadditive effect of joint drug administration can also be called as potentiation.
y. Adrenaline through G-P-CRs causes hyperglycaemia.
z. Transduction mechanisms through $IP_3$ result in excitation, contraction or secretion.
aa. Competitive antagonism is also called as reversible or surmountable antagonism.
bb. Noncompetitive antagonism is also called as irreversible or unsurmountable antagonism.
cc. Batrachotoxin, veratridine or scorpion venom causes persistent depolarization.
dd. Local anaesthetics prevent depolarization of sensory nerves.
ee. The action of a prodrug is enzymatically mediated.
ff. Drug effects after iv injection are terminated rapidly as compared to im or sc injection.
gg. SC implants ensure long duration of pharmacological effects.
hh. Latency after oral administration of a dug is longest.
ii. Latency following iv injection of a drug is practically nil.
jj. Therapeutic ration is a better index of drug safety than therapeutic index.
kk. A potent agonist can still produce maximal response when most of its receptors are occupied by an antagonist.
ll. Drug-Receptor interaction implies lock and key system.
mm. Drug mechanism of action is also non-receptor-mediated.

# Chapter 5 : FACTORS MODIFYING DRUG RESPONSES

A variety of factors, either singly or in combination, influence the pharmacological response (effects) following drug administration.

1. **Species variation**: The effects of a drug vary in different species. Morphine causes CNS depression in man and dog, but CNS excitation in cat. Invertebrates are resistant and poultry are less susceptible to strychnine convulsions as compared to dogs. Belladonna leaves (atropine) are toxic to all animals, except rabbit (atropinase in liver inactivates atropine). Intensity of drug effects following oral administration vary in ruminants and nonruminants (differences in absorption). Some drug metabolizing reactions vary from species to species (Cats are deficient in glucuronyl transferase necessary for glucuronidation of salicylates).
2. **Individual variation**: Drug response varies due to normal biological variation among individuals of same species, as governed by genetic factors. Temperament also determines the drug responses. Ferocious (high-strung) or excited animals need a higher dose of a CNS depressant than dull or docile animals. Thoroughbreds need relatively larger drug doses (tranquilizers) than nondescript animals
3. **Age**: Newborn/very young and old are more sensitive to drugs than the normal adults. In young the organs of metabolism and excretion are not fully functional and in old these organs function below the normal levels. Young or old animals require relatively a smaller dose than the adults do.
4. **Sex**: In general the variation in gender responses to drugs is minimal. However, females are more sensitive than males to some drugs. Female rats are two times more susceptible to the rodenticide red squill than male rats. The variation in sex influenced drug responses is due to hormonal differences (influencing enzymatic processes: metabolism). The resistance of males is due to presence of high levels of testosterone.
5. **Body weight**: It reflects the extent of tissues that is exposed to the action of drugs. Therefore, the dose of a drug in an animal is based on its body weight. While computing drug dosage in ruminants, the weight of ruemen contents should be considered. Similarly, in ruminans, the extent of dilution of the drug by ruminal fluids and ingesta must also be kept in mind especially while oral dosing. The weight of fetus during pregnancy, fat deposits in obese animals and fluid in oedematous conditions should also be considered, while determining the dose of the drug to be administered.
6. **Drug dosage form**: Liquid dosage forms are more rapidly absorbed and produce effects quicker than the solid dosage forms. In case of solids or powders, the size of particle influences the rate of absorption (smaller the size quicker will be the absorption). Drugs in aqueous solutions are more rapidly absorbed than in oily solutions after IM injection. For promotion of fecal excretion of ingested toxicants from the GIT, saline purgatives are usually recommended instead of oily purgatives (like vegetable oils), which may increase the toxicity through elevated absorption of lipid soluble toxicants like pesticides.
7. **Dose of the drug**: Drug effects are related to bioavailability, which in turn is dependent on dose. At therapeutic doses drugs selectively produce desired response, but at higher doses the selectivity is lost, producing toxicity or adverse effects.
8. **Time of administration**: CNS depressants show less effect when administered in morning hours as compared to evening hours. Ingested drugs are rapidly absorbed and result in rapid onset of action on empty stomach (more true for carnivora, which have a short and efficient digestive tract than herbivora). Time of administration is of little importance in ruminants, since rumen is always partly full with ingesta.
9. **Route of administration**: Onset of drug effects by different routes of administration is in the order of IV > IM > IP > SC > oral. The rate and extent of absorption and pattern of biotransformation differ with the route of administration, directly altering the drug responses. Therefore, drug dosage need to be adjusted according to the route. Usually the iv dose of a drug is smaller than sc dose, which is lesser than the oral dose. Inhalation of volatile drugs also results in rapid onset of systemic effects

due to prompt absorption through pulmonary alveolar epithelium. Buccal administration (lingual or sublingual) avoids inactivation of the drug in GIT and ensures satisfactory absorption. Normally, drugs do not produce significant systemic effects when applied locally (eye, ear, skin, uterus etc), if the topical tissue layers are intact. The veterinarian is posed with a variety of problems when oral administration of drugs in animals is considered. In ruminants orally administered drug may fail to produce satisfactory systemic effects (drug dilution by huge ruminoreticular contents and metabolism by ruminal microflora). Among monogastrics, the responses of orally administered of drugs can be better (reasonably) predicted in carnivores than in herbivores, as the former have a short and relatively more efficient digestive tract as compared to the latter.

10. **Drug Absorption**: The responses of a drug are directly related to its absorption, which in turn is influenced by route of its administration. Degree of vascularity at the site of administration alters the rate of absorption. Absorption is decreased/delayed when the capillaries at the site are constricted. The pKa of the drug and pH of the medium also affect absorption.
11. **Distribution of Drug**: The effect of a drug on a particular organ or tissue is related to the concentration of the drug entering the organ/tissue. Some drugs have special affinity to certain tissues (iodine in thyroid; DDT or barbiturates in fat depots etc). Drug accumulation in body tissues is important from toxicity point of view, particularly in case of cumulative toxicants like DDT, lead, mercury etc: Cumulative poisons). Drugs stored in fat depots are slowly released causing sustained effect, but when lipolysis occurs such drugs may show toxicity.
12. **Protein Binding of Drug**: If a drug is bound extensively to the plasma proteins, is effects are reduced. It also lowers tissue penetration, metabolism and excretion of drugs. Effects of such high protein affinity drugs are magnified in disease states characterized by hypoproteinaemia. Similarly, the effects of such high protein bound drugs are greatly increased when they are displaced from protein binding by other drugs (About 95% of warfarin is bound to plasma proteins, it shows toxicity reactions if phenylbtazone is administered, which displaces warfarin from bound state).
13. **Metabolism of Drug**: The drug effects gradually vanish over a period of time after absorption due to elimation of the drug (metabolism and excretion). However, some drugs get activated through metabolism (prodrugs). Enzyme induction and enzyme inhibition also alter drug metabolism and the drug responses (see drug metabolism: Functions of metabolism). Hepatic diseases prolong drug effects due to defective metabolism of the drug. Intestinal and ruminal microflora also have drug metabolizing enzymes and alter responses of orally administered drugs (Release of sulfathiazole from gut-active sulfonamides, activation of anthraquinone glycosides as purgatives, liberation of free drug from glucuronide conjugates in intestines, reduction of nitrate to nitrite, liberation of free ammonia from urea, reduction of parathion to aminoparathion etc).
14. **Excretion of Drug**: Drug effects are prolonged when excretory mechanisms are defective (renal and/or hepatic insufficiencies). Excretion of a drug may also be altered by other drugs (see drug interactions). If a drug metabolite (glucuronide conjugate) is mainly excreted through bile into intestines, its hydrolysis by intestinal microflora liberates active/free drug, which is reabsorbed (enterohepatic cycle) and its effects are prolonged till it is completely excreted through kidney.
15. **Health status**: Weak, emaciated or debilitated animals (low metabolic status of liver due to low glycogen stores) are more sensitive to drugs than the normal/healthy animals. Fatty animals require more dose of a fat soluble drug than the lean animals. The effects of orally administered drugs are lowered in diarrhoea and enhanced in constipation due to decrease and increase in absorption respectively. Drug effects are intensified in hepatic and renal diseases (impaired metabolism and excretion) and protein deficiency (hypoalbuminaemia: low protein binding).
16. **Tolerance**: Failure of an animal to respond to the usual therapeutic dose is called drug tolerance, resistance or fastness. It may be **natural** or **acquired**. Natural tolerance is similar to species variation. Acquired tolerance appears due to repeated and/or continuous exposure to a drug (CNS depressants: morphine, barbiturates, tranquilizers etc.). It is due to refractoriness (adaptation) of the tissues (receptors) to the continuous presence of the drug. The tolerance of chronic alcoholics to usual doses of alcohol may be called **pseudotolerance** (retarded absorption of alcohol due to

resistance - drug fastness -

thickening of GI mucosa). Pathogenic microorganisms also acquire resistance (drug fastness) to antimicrobials following continuous exposure to the antimicrobials (especially at sub-therapeutic doses). The tolerance of microorganisms to antimicrobial drugs is called as resistance (or drug fastness commonly shown by *Staphylococcal* bacteria). The bacteria showing resistance (drug fastness) to any one antibiotic of a chemically related group also exhibit insensitivity to other members of the group; this is called **cross-resistance** (tetracyclines, sulfonamides etc due to similar mode of antibacterial action). Animals may also develop cross-tolerance to phenothiazine tranquilizers (similar pharmacological action/effects).

16. Tachyphlaxis is a phenomenon, where there is gradual decrease of pharmacological respone due to a drug when it is administered repeatedly (at the same dose) at short intervals, similar to tolerance, but it is different rom tolerance as described above. This is a rapid and reversible phenomenon. Tachyphlaxis is observed with tryramine or ephedrine on cat BP.

17. **Idiosyncracy**: It is an abnormal drug response, genetically mediated, in sensitive individuals

18. **Drug Interactions**: Administration of more than one drug is essential in the treatment of certain diseases. Improper combination of drugs can lead to undesirable pharmacological consequences (failure of therapy or adverse/toxic reactions). The drug interactions can occur outside the body (before administration), or within the animal's body.

a. **Drug Interactions outside the body**: This is generally referred as drug incompatibility. The examples of *in vitro* drug interactions are:
   i. Mixing oil and water without adding a stabilizer.
   ii. Mixing alkaloids with acids or other drugs.
   iii. Mixing alkalies with acids.
   iv. Mixing sulfonamides in dextrose solution (precipitation).
   v. Mixing tetracyclines and penicillins (precipitation).
   vi. Mixing oxidizing and reducing agents.

b. **Drug Interactions inside the body**: When two drugs are administered simultaneously or one soon after the other (within a short interval) the pharmacological effect of one drug may be altered by the other drug. This is called drug interaction inside the animal body, which may be pharmacokinetic (absorption, distribution, protein binding, metabolism and excretion) or pharmacodynamic reasons (synergism, and antagonism). The *in vivo* drug interaction may result in beneficial and/or harmful effect on the animal.

**Pharmacokinetic Interactions:**

**A. Interactions during Absorption**:

i. Prolongation of local anaesthetic action by adrenaline: Delayed absorption.
ii. Failure of absorption of orally administered tetracyclines in animals treated with metallic compounds (formation of insoluble chelates).
iii. Oral antibiotic therapy prolongs anticoagulant effect of oral anticoagulants (impairs bacterial synthesis of vitamin K).

**B. Interactions during Distribution**: When a drug extensively bound to plasma proteins (80%) is displaced from the binding by another drug, the effects of the former will be greatly enhanced.

i. Displacement of warfarin by phenylbutazone.
ii. Displacement of methotrexate by sulfonamides and salicylates.
iii. Phenylbtazone, frusemide, digitoxin, propranolol, diazepam and quinidine are extensively bound to plasma proteins (high affinity). Effects of these drugs will be enhanced if they are displaced from protein binding.

**C. Interactions during Metabolism**: Any process that interferes with drug metabolism can increase or dcrease the drug effects. This is due to induction or inhibition of hepatic microsomal drug metabolizing enzymes (see drug metabolism). Lipid soluble drugs if continuously administered become enzyme inducers. Enzyme induction not only alters drug metabolism, but also interferes with physiological function of hormones (thyroxine, steroid hormones etc which are the endogenous substrates of the induced enzymes).

i. Barbiturates and chloral hydrate increase hydroxylation of coumarin derivatives.
ii. Barbiturates stimulate metabolism of DDT and griseofulvin.
iii. Inhibition of tolbutamide and antipyrine metabolism by chloramphenicol
iv. Blockade of alcohol metabolism by disulfiram (antabuse)

**D. Interactions during Excretion**: Interactions occur due to facilitation or impairment of renal excretion of drugs or drug metabolites. Simultaneous administration of two drugs that are excreted by carrier-mediated process results in impairment of excretion of less rapidly transported metabolite.

i. Probenecid inhibits renal excretion of penicillin G.
ii. Urinary alkalinization increases excretion of sulfisoxazole, salicylates and Phenobarbital.
iii. Urinary acidification promotes amphetamine excretion.
iv. Dicoumarol impairs tubular secretion of chlopropamide.

**Pharmacodynamic Interactions:**

This is also considered as pharmacological incompaiblity. Occur due to action of drugs at a common receptor site or at different sites leading to increase or decrease in response to a drug:

i. Enhanced alpha-adrenoceptor blockade by phenoxybenzamine with other adrenergic blockers.
ii. Increase in muscarnic receptor blockade by anticholinergics.
iii Enhanced neuromuscular blockade by dTC under ether anaesthesia or by amino glycoside antibiotics.
iv. Prolonged CNS depression following morphine and barbiturate injections.
v. Neutralization of vasoconstriction of adrenaline by nitrites

## EXERCISE

1. Enlist the factors modifying the drug responses. Discuss how the responses of an orally administered drug are altered.
2. Describe how the drug effects are altered by pharmacokinetic considerations with suitable examples.
3. Describe how animal-related considerations alter the drug responses.
4. What do you mean by drug interactions? Discuss the *in vitro* and *in vivo* drug interactions.
5. Describe pharmacokinetic drug interactions with suitable examples.
6. **Write short note on the following**:
   a. Pharmacodynamic interactions
   b. *In vitro* drug interactions
   c. Pharmacokinetic interactions
   d. Tolerance
   e. Species variation in drug effects
   f. Route of administration and drug responses
7. **Differentiate between the following**:
   a. Natural tolerance & Acquired tolerance
   b. *In vitro* & *In vivo* drug interactions
   c. Pseudo tolerance & Cross tolerance
   d. Tolerance & Tachyphylaxis
   e. Tolerance & Drug fastness
   f. Drug responses after oral administration in monogastrics & ruminants
8. **Give the most appropriate reason for each of the following statements in one or two sentences**:
   a. Rabbits are resistant to belladonna toxicity.
   b. Cats are highly sensitive to salicylates.
   c. Hypoprotinaemia magnifies drug effects.
   d. Adrenaline prolongs local anaesthesia.
   e. Tachyphylaxis is similar and dissimilar to tolerance.
   f. Poultry are relatively resistant to strychnine convulsions.

g. Strychnine convulsions are not seen in invertebrates.
h. Liquid dosage forms produce effects rapidly as compared to solid dosage forms.
i. Protein drugs are ineffective after oral administration.
j. Vegetable oil purgatives are contraindicated in pesticide toxicity.
k. Drug responses following oral administration are better predicted in carnivores than in herbivores.
l. Drug responses following oral dosing in ruminants will be erratic.
m. Continuous oral antibacterial therapy prolongs anticoagulant effect of oral anticoagulants.
n. Bacteria developing drug fastness against one sulfonamide also become resistant to other sulfonamides.
o. Drug effects of orally administered drugs are increased in constipation.
p. Drug effects of orally administered drugs are lowered in diarrhea.
q. Drug effects are increased in hepatic insufficiency.
r. Drug effects are increased in renal impairment.
s. A drug following local application generally does not produce systemic effects.

9. **What do you mean by the following**:
a. Tolerance
b. Cross resistance
c. Natural tolerance
d. Drug resistance
g. Drug fastness
h. Tachyphylaxis
i. Pharmaceutical incompatibility
j. Pharmacological incompatibility

# Chapter 6 : ADVERSE DRUG REACTIONS AND DRUG TOXICITY

A drug can produce a beneficial effect, adverse or side effect and toxic effect as governed by several factors, more so in Veterinary Pharmacology than encountered in Medical Pharmacology, The reason is that drug effects are not uniform among different species (see factors modifying drug effect).

An **adverse effect** or **side effect** of a drug may be defined as an unwanted effect following administration of a drug in treating a disease state. The adverse or side effect due to a drug can be either due to its main pharmacological effect, unrelated to its main pharmacological effect. The adverse effects of a drug can be predicted when its actions on different systems of body are known (cardiac arrhythmia due to cardiac glycosides, sedation with anti-anxiety drugs, hypoglycaemic crisis with insulin, morphine-induced dependence, dryness of mouth with atropine, superinfection and B-complex vitamin deficiency following oral broad spectrum therapy in ruminants etc.). The examples of drug-induced adverse effects unrelated to its pharmacological action include : Sulfonamide-induced neprotoxicity in dogs/cats, ototoxicity and nephrotoxicity with aminoglycoside antibiotics, aspirin-induced bleeding, NSAIDs-imduced peptic ulcer, teratogenicity with thalidomide, sedation following use of antihistamins in allergy, constipation following use of opioids as analgesics or antitussives etc.

A drug after entering in systemic circulation may have pharmacological effects on different systems of the body. If a drug is administered for a desired effect on a particular system, its effect on other system may be called as a side effect (which cannot be avoided). Examples: Morphine use as analgesic also results in constipation, long term oral broad spectrum antibiotic therapy leads to deficiency of B-complex vitamins, CNS depression due to use of antihistamines and hypokalaemia due to long term use of diuretics. Sometimes, a drug is given for a specific (life saving) purpose, but it produces unavoidable undesirable side/adverse effects (sometimes called toxicity), the examples are renal toxicity with sulfonamides, vestibular and ototoxicity with streptomycin etc.

A **toxic effect** usually appears following when a drug is inadvertently administered at a high dose and/or for prolonged period than clinically required (drug toxicity, see below).

**Mutagenecity**: Ability of a toxicant (Mutagen) to cause mutation. Mutation is alteration in genotype of a cell by modification of DNA (Aflatoxins). Mutations in proto-oncogenes, which regulate cell growth and tumour supressor genes result in carcinogenesis.

**Carcinoigencity**: Ability of a chemical (Carcinogen) to interact with DNA and cause cancer (Aflatoxins).

**Teratogenecity**: Ability of a drug/chemical (Teratogen) to induce structural malformations in the developing foetus, when exposed in early pregnancy (Aflatoxins, thalidomide, warfarin, steroid hormones, all anticancer drugs).

**Iatrogenic effect**: (Greek Iatros = physician) Appearance of a pathological condition/reaction due to drug administration, which persists after discontinuation and/or excretion of the drug (Prolonged oral use of glucocorticoids, aspirin or indomethacin may precipitate development of peptic ulcer in dogs).

**Idiosyncrasy**: Genetically determined abnormal reaction to drugs in certain races (hemolytic anaemia in black males following primaquine due to deficiency of eryhthrocytic glucose-6-phosphate dehydrogenase).

**Allergic reaction (Hypersensitivity)**: It is an acute adverse reaction that results from prior sensitization to a drug or chemically related substance or a foreign protein. Drug allergy is unpredictable. The reaction may occur due to prior sensitization to a drug in sensitive individuals. Allergic reaction like anaphylaxis is immunogenic, which may be induced by a drug after its binding to an endogenous protein. The complex behaves like a hapten (allergen or antigen) and produces antibodies in sensitive subjects. Such an individual following subsequent exposure to the drug will show allergic reaction (rash/urticaria, sneezing, asthmatic attacks, eosinophilia etc). The drug itself may not be immunogenic. The drugs that can cause allergic reaction are penicillins, aspirin, allopurinol, sulfonamides etc.

**Anaphylaxis**: An anaphylactic reaction occurs when a sensitive animal is exposed to a protein (egg albumin) to which it had been prior sensitized. First exposure to the protein does not cause any reaction, but the second or subsequent exposures (repeated) to the same protein causes severe systemic allergic reactions, which may be fatal (intense bronchoconstriction and CV shock).Anaphylactic reactions may be induced by penicillins, asparaginase, corticotrophin, heparin etc. The signs and symptoms of allergic and anaphylactic reactions are due to endogenous release of histamine, leukotrienes and other mediators of inflammation. In severe allergic and anaphylactic reactions prompt treatment with adrenaline, corticosteroids, antihistamines and fluids is life-saving:

**Drug Toxicity**: Toxicity refers to inherent capacity of a substance to cause harmful effect. Drugs under special circumstances (indiscriminate use: dose, frequency, and mode of administration or individual variation) also cause toxicity: Drug toxicity is of three types: **Acute, sub-acute and chronic.**

**Acute toxicity** results from intake of large dose within a short period (mostly single large dose), where the animal shows toxic signs and symptoms depending upon the drug and if not attended promptly the animal may die. Experimental acute toxicity of a drug is conducted to find out its toxic potency by calculating the $LD_{50}$ (dose killing 50% of the exposed population).

**Sub-acute toxicity** results from continued or repeated exposure to low doses of the drug (sub-toxic level) daily over a period of 90 days. Toxicity resulting from continued exposure to still smaller doses over a period of six months or more is called **chronic toxicity**. In both sub-acute and chronic toxicities, animals may not immediately reveal visible toxic signs or symptoms, but only after the level of drug reaches a critical level in the body i.e. due to accumulation. The chemicals that cause sub-acute or chronic toxicity are called as cumulative poisons (which accumulate in the body). These toxicities are characterized by changes in haematological and biochemical profiles and development of histopathological changes (even cancer/tumor) in internal organs. Normally these changes do not appear in acute toxicity (animal dies very fast).

**Chronicity Factor** is the ratio of the acute $LD_{50}$ (high single dose) to chronic $LD_{50}$ (repeated exposure to small doses for 90 days or so). It is derived from the equation: Acute $LD_{50}$ ÷ Chronic $LD_{50}$. By noting the chronicity factors of different drugs, their relative cumulative action can be assessed. Higher the chronicity factor more the drug is cumulative.

## EXERCISE

1. Write a short note on drug toxicity.
2. **What do you mean by the following?/ or Define the following**:
   a. Adverse effect
   b. Side effect
   c. Toxic effect
   d. Mutagenicity
   e. Teratogenecity
   f. Carcinogenicity
   g. Mutagen
   h. Teratogen
   i. Carcinogen
   j. Iatrogenic effect
   k. Idiosyncracy
   l. Allergic reaction
   m. Hypersensitivity
   n. Anaphylactic reaction
   o. Acute toxicity
   p. Subacute toxicity
   q. Chronic toxicity
   r. Chronicity factor
   s. Cumulative toxicant/drug
3. **Differentiate between the following**:
   a. Adverse effect & Side effect
   b. Toxic effect & Side effect
   c. Iatrogenic effect & Idiosyncracy
   d. Allergy & Anaphylaxis
   e. Therapeutic effect & Toxic effect
   f. Acute toxicity & Subacute toxicity
   g. Subacute toxicity & Chronic toxicity
   h. Measures of acute and cumulative toxicities
4. **Give the most appropriate reason for each of the following statements in one or two sentences**:
   a. Side effect of a drug cannot be avoided.
   b. Dose is a determining factor of the drug effects on the host.
   c. Acute toxicity helps in knowing the toxic potency of a drug.
   d. The toxic effects are not immediately seen during subacute/chronic toxicity.
   e. The onset of signs and symptoms in subacute/chronic toxicity is delayed.
   f. Acute toxicity is characterized by rapid onset of toxicity signs and symptoms.
   g. Cumulative drugs generally cause chronic/subacute toxicity.
   h. Characteristic/Pathognomonic haematobiochemical or histopathological changes are not seen in acute toxicity.
5. **Explain the following with appropriate examples**:
   a. Side effect b. Allergic reaction c. Anaphylactic reaction d. Toxic effect

# SECTION II : ANS PHARMACOLOGY

## Chapter – 7: PHYSIOLOGICAL (GENERAL) CONSIDERATIONS

The somatic nerves control the voluntary functions of the body i.e. movements through their innervation to skeletal muscles. Whereas the autonomic nerves control the involuntary functions of the body through their innervation to smooth muscles of visceral organs and cardiac muscle. As the visceral organs exhibit a degree of autonomy, their nerve supply is named as autonomic nervous system (ANS) by Langley (1908). The ANS is also called as visceral nervous system or involuntary nervous system.

| Differences between | Somatic Nervous System (SNS) | Autonomic Nervous System (ANS) |
|---|---|---|
| a. **Supply to Organs:** | Skeletal muscles | All visceral organs |
| b. **Location of Synapse:** | Within the CNS | Outside the CNS |
| c. **Myelination:** | Myelinated | Preganglionic myelinated, but post-ganglionic nerve nonmyelinated |
| d. **Formation of plexuses:** | Absent | Present |
| e. **Transmitter:** | Acetylcholine | Acetylcholine & Noradrenaline |
| f. **Effect of dennervation:** | Loss of function. Muscles paralysed/atrophied | Spontaneous activity. Organs exhibit intrinsic activity |

The functions of the body, both voluntary or involuntary, are regulated by stimuli from different centres in CNS and the impulses thereof are conveyed through nerve junctions and between nerves and organs (neuroeffector organ junction) by a process called neurohumoral transmission.

### Neurohumoral Transmission (NHT)

The NHT is an electrochemical process involving impulse conduction and impulse transmission. The passage of an impulse along the length of an axon is called impulse conduction; whereas, passage of an impulse through nerve-nerve junction or neuro-effector junction is called impulse transmission.

#### 1. Impulse Conduction

Subsequent to a stimulus the resting membrane potential (RMP = - 70–75 mv, polarized state) changes to positivity due to influx of $Na^+$ into the axon across the neuronal membrane from the extracellular fluid and inside of the nerve membranes turns positive (**depolarization**). Then the $K^+$ followed by $Na^+$ come out of the nerve through activation of sodium pump (**repolarization**). At this point there exists a state of more negativity (than the RMP i.e. negative after potential) in side the nerve membrane (**hyperpolarization**), which returns to RMP once the $K^+$ reenter into the axon. All these changes contribute to **nerve action potential (NAP)**.

The transmembrane ionic currents across the nerve membrane produce local circuit currents around the axon and the localized area of the nerve gets excited (stimulated). The excited portion of the axon then activates the adjacent portion of nerve membrane and thus the NAP is propagated up to the nerve ending uninterrupted, completing the process of axonal conduction. The impulse from the nerve terminus is transmitted to another nerve and/or the effector cells of the organ by means of transmission.

The axonal conduction is blocked by tetrodotoxin (puffer fish toxin) and saxitoxin (shellfish toxin) which interfere with $Na^+$ entry into nerves, thus blocking depolarization and generation of NAP. Local anaesthetics also act in similar fashion. Batrachotoxin (toxin of South American frog) increase $Na^+$ entry into the nerve, causing persistent depolarization and blocking axonal conduction.

#### 2. Impulse Transmission

The impulse transmission is mediated by neurohumoral transmitters. The pioneering hypotheses and experimental evidences of Dubois Raymond (1877), Kuhne (1888), Elliot (1904), Langley (1905) and Dixon (1906), Otto Loewi (1921), Otto Loewi and Navratil (1926) and von Euler (1946) illustrated and confirmed the involvement of transmitters in impulse transmission. The process involves several steps as below:

a. **Release of the Transmitter:** When the impulse (NAP) reaches the nerve terminal, the transmitter chemical stored in the synaptic vesicles is released in the synaptic junction (nerve-nerve) or neuroeffector junction (nerve-organ) from the terminal. The release occurs through exocytosis involving $Ca^{++}$ The transmitters in ANS are acetyl choline and Norepinephrine and in SNS is acetyl choline.

b. **Combination of the Transmitter with Post-Junctional Receptors and Initiation of Post-Junctional Activity:** The transmitter released into the junctional cleft (nerve-nerve or nerve-effector cell) instantly combines with the receptors present on the post-junctional membrane (nerve or effector cell), causing localized increase in ionic permeabilities. When there is increase in $Na^+$ permeability, localized depolarization occurs causing excitatory post-synaptic potential (**EPSP**). When there is selective increase in $K^+$ or $Cl^-$ permeability localized hyperpolarization causing in inhibitory post-synaptic potential (**IPSP**).

c. **Propagation of Post-Junctional Activity:** When EPSP is generated, it initiates a propagated NAP in the post-junctional nerve or MAP in the muscles causing spontaneous depolarization of the nerve or propagation of the impulse resulting in increase tone and motility, contraction or secretion. When an IPSP is initiated, it opposes the simultaneous excitatory potentials at the post-junctional site. If the IPSP is more than the EPSP, it results in inhibition or depression of the post-junctional nerve or effector cell. If the IPSP is less than the EPSP, it results in stimulation or excitation of the post-junctional nerve or effector cell.

d. **Destruction or Removal of the Transmitter:** After the transmitter serves its function (reacting with the post-junctional receptors) it is either destroyed (enzymatically: Acetyl choline by AChE and Norepinephrine by COMT) or removed from the site through re uptake into the nerve terminal diffuses away.

The autonomic nervous system comprises of two divisions: The parasympathetic system and the sympathetic system.

| Differences between | Sympathetic Nervous System | Parasympathetic Nervous System |
|---|---|---|
| 1. **Origin:** | Thoracolumbar | Craniosacral |
| 2. **Distribution:** | Wide | Limited |
| 3. **Ganglia:** | Away from organ | Near or on organ |
| 4. **Post-ganglionic Nerve:** | Long | Short |
| 5. **Ratio of Pre to post-ganglionic Nerves:** | Many | Mostly 1 : 1, except in Aeurbach's plexus (intestines) |
| 6. **Transmitter:** | Noradrenaline & Acetylcholine | Acetylcholine |
| 7. **Stability of Transmitter:** | Relatively stable | Unstable |
| 8. **Major Functions:** | Tackles stress : fight or flight, expenditure of energy, increase in muscle, CV and respiration activities, vasodilatation (muscle) etc. | Assimilation of food, conservation of energy, Decrease CVS, constrict bronchioles, increase GI activity |

The coordinated working of sympathetic and parasympathetic systems is referred as "**Yin-Yang effect**": The actions of one system tend to oppose the actions of the other.

The NHT involving acetyl choline (ACh) is called cholinergic transmission and that of Norepinephrine (noradrenaline or NorA) is called adrenergic transmission. The ANS is physiologically grouped into two functionally distinct divisions: Parasymathetic System and Sympathetic System, whose functions are regulated through cholinergic and (mainly) adrenergic transmission respectively.

## Chapter – 8: CHOLINERGIC TRANSMISSION / Parasympathetic

The sites where ACh is a transmitter include:

a) Autonomic ganglia, both sympathetic and parasympathetic
b) Parasympathetic post-ganglionic nerve terminals
c) Sympathetic post-ganglionic nerve terminals to sweat glands in man and cats
d) Nerve supply to adrenal medulla
e) Central synapses (CNS, both brain and spinal cord)
f) Somatic motor nerve endings, neuromuscular junction (MEP)

**Synthesis of ACh**: ACh synthesis occurs in axons, which requires choline and acetate. Choline is taken into the nerve cell from the extracellular fluid and acetate is formed within the nerve cell itself. Formation of ACh occurs through the following reactions:

| | | | | |
|---|---|---|---|---|
| Acetic acid | + | ATP | Acetate thiokinase → | Acetyl AMP |
| Acetyl AMP | + | CoA | Transacetylase → | Acetyl CoA |
| Acetyl CoA | + | Choline | Acetyl transferase → | ACh and CoA |

Choline is transported into the nerve by a carrier. Hemicholinium and triethylcholine competitively block choline uptake into the nerve and thus interferes with synthesis of ACh.

**Storage and Release of ACh**:
After synthesis in the axoplasm, ACh is transported (carrier-mediated) into synaptic vesicles and stored until it is required to be released. When the AP reaches the nerve terminal $Ca^{++}$ enter the nerve terminal and cause contraction of the filaments connecting the synaptic vesicular membrane to the nerve membrane, thus pulling the synaptic vesicle in close proximity to nerve terminal membrane and fusion of both vesicle membrane and nerve membrane. Then ACh comes out of the nerve terminal (pre-junctional membrane) by exocytosis.

Vesamicol competitively inhibits uptake of ACh into the vesicles. Botulinum toxin and β-bungarotoxin block ACh release at neuromuscular junction and thus cause paralysis of respiratory muscles. The black widow spider toxin and ciguatoxin cause an initial increase followed by blockade of ACh release.

The released transmitter combines with specific post-junctional receptors called cholinergic receptors (nerve or effector cell). The pre synaptic release of ACh (at autonomic neuroeffector junction) is controlled by ACh itself released from the same nerve terminal (autoinhibition) and NorA released from sympathetic nerves i.e. homotropic and heterotropic pre synaptic interactions, respectively.

**Cholinergic Receptors:**
These are of two types: Muscarinic and nictonic receptors which are named after muscarine (alkaloid of mushroom *Amanita muscaria*) and nicotine (alkaloid of leaves of *Nicotiana tabacum*), respectively. These are further divided into different sub-types. The sites, agonists and antagonists of these receptors are as under:

**Muscarinic Receptors (M):**

| Subtype | Location | Agonists | Antagonists |
|---|---|---|---|
| $M_1$ | CNS, glands (gastric, salivary etc) and autonomic ganglia | ACh, carbachol, oxotremorine and McNA343* | Atropine, dicycloverine, ipratropium, tolterodine, oxybutynin, pirenzepine* and Mumba toxin MT7* |
| $M_2$ | CNS, heart and GIT | As for M1 Methacholine | Atropine, dicycloverine, tolterodine, oxybutynin, ipratropium, and Gallamine* |
| $M_3$ | Exocrine glands (gastric, salivary etc) and smooth muscles (GIT, eye and blood vessels) | As for M1 Bethanechol | Atropine, dicycloverine, tolterodine, oxybutynin and ipratropium |
| $M_4$ | CNS and lung | As for M1 | Atropine, dicycloverine, tolterodine, oxybutynin, ipratropium and Mamba toxin MT3* |
| $M_5$ | CNS, salivary glands and eye (iris and ciliary muscle) | As M1 | Atropine, dicycloverine, tolterodine, oxybutynin and ipratropium |

* Selective

The muscarinic receptors are G-protein coupled receptors ($M_1$, $M_3$ and $M_5$ activate Gs protein; whereas, $M_2$ and $M_4$ receptors activate Gi protein).

**Nicotinic Receptors (N):**

| Subtype | | Location | Agonists | Antagonists |
|---|---|---|---|---|
| Skeletal Muscle | | Neuromuscular junction (post-synaptic) | ACh, carbachol, suxamethonium, PTMA | d-tubocuraine, pancuronium, hexamethonium and α-conotoxin |
| Ganglion | | Autonomic ganglia (post-ganglionic) | ACh, carbachol, nicotine, epibatidine and DMPP | Mecamylamine and trimethaphan |
| CNS | A | Brain (pre and post-synaptic) | Nicotine, epibatidine ACh and cytosine | Mecamylamine, methylaconitine and α-conotoxin |
| | B | Brain (pre and post-synaptic) | Epibatidine and DMPP | Methylaconitine and α-bungarotoxin |

Nicotinic receptors are ligand-gated ion channels, activation of which results in depolarization and excitation.

**Destruction of ACh:**

After serving transmitter function (reacting with post-junctional receptors and initiation of post-junctional activity), ACh is instantly destroyed in a flash like suddenness by the action of an enzyme acetylcholinesterase (AChE), which is present in all cholinergic neuronal sites. It hydolyzes ACh into acetic acid and choline. AChE is also present in RBC membrane, where its exact function is not known, it may regulate erythrocyte permeability. AChE is called true cholinesterase (ChE). Another type of ChE is butyryl-ChE (BChE) or pseudo ChE. It is a nonspecific esterase, mainly present in blood plasma, liver and other organs. AChE hydrolyzes ACh at a faster rate than other choline esters including methacholine, but not benzoylcholine or butyrylcholine. AChE and BChE also inactivate substance P. BChE rapidly hydrolyzes butyrylcholine and benzylcholine, slowly ACh, but not methacholine. BChE also hydrolyzes other esters (procaine, suxamethonium and propanidid). Both the enzymes are inhibited by anticholinesterase agents such as organic phosphate insecticides, whose toxicity is characterised by excessive accumulation of ACh. The pharmacological effects of drugs like neostigmine and physostigmine are due to inhibition of AChE, the indirectly acting cholinergics (see under cholinergic drugs).

Q1. Write the synthesis, storage, release, fate & pharmacological action of epinephrine.

# Chapter – 9: NORADRENERGIC/ADRENERGIC TRANSMISSION

Q1

The transmission mediated by noradrenaline or norepinephrine at post-ganglionic sympathetic nerve terminals (except sweat glands in man and cats) and that of norepinephrine and dopamine in CNS is called adrenergic transmission.

**Synthesis of NorA:** Synthesis of norepinephrine occurs in adrenergic nerves. L-Tyrosine, an aromatic amino acid, the precursor of norepinephrine is taken from the extracellular fluid into the adrenergic nerves. The steps involved in biosynthesis of norepinephrine are:

Phenylalanine hydroxylase

Tyrosine ( ← Phenylalanine)

Rate limiting step ↓ Tyrosine hydroxylase

Dihydroxy phenylalanine (DOPA)

↓ DOPA decarboxylase

**Dopamine**

↓ Dopamine β-hydroxylase

**Norepinephrine**

In adrenal medulla ↓ Phenylethanolamine N-methyltransferase

**Epinephrine**

Tyrosine is formed in liver from the essential amino acid phenylalanine by the action an enzyme hydroxylase. The DOPA decarboxylase also catalyzes decarboxylation of L-aromatic amino acids L-histidine and L-tryptophan in biosynthesis of histamine and 5-hydroxytryptamine respectively (see under 'Autacoids'). The synthesis up to dopamine occurs in the axoplasm (cytosol). Formation of norepinephrine occurs in the synaptic vesicles in the adrenergic nerves. Dopamine enters the synaptic vesicles, where it is hydroxylated to norepinephrine by dopamine β-hydroxylase which is a membrane bound enzyme in the synaptic vesicles. α-methyltyrosine inhibits tyrosine hydroxylase and blocks norepinephrine or epinephrine synthesis (clinical application in treating inoperable phaeochromocytoma in man). Carbidopa, a derivative of DOPA, an inhibitor of DOPA decarboxylase is used in treating Parkinson disease in man. α-methyldopa is processed like dopa to form α-methyldopamine, which ultimately results in formation of α-methylnorepinephrine (false transmitter of norepinephrine) and loss of neurotransmitter function of adrenergic nerves.In adrenal medulla, which has two types of chromaffin granules one having norepinephrine and the other epinephrine. Norepinephrine formed in the one type of granules leaves into the cytosol, where it is methylated to form epinephrine, which enters into other granules. The reaction is catalyzed by phenylethonalamine N-methyltransferase, mainly found in adrenal medulla and in CNS, where epinephrine serves transmitter function.

**Storage and Release of NorA:**

In adrenergic nerves norepinephrine is stored in synaptic vesicles along with ATP (in 1:4) and a protein chromogranin. Reserpine prevents transport of norepinephrine into the vesicles by binding to the norepinephrine carrier protein. In adrenal medulla epinephrine is stored in chromaffin cells. When the adrenergic nerve terminal gets depolarized (i.e. when the AP reaches), influx of Ca++ triggers norepinephrine release through exocytosis.

Norepinephrine release is controlled pre synaptically by neurotransmitters, including NorA itself and neuromodulators, whose receptors are located presynaptically at adrenergic nerve terminals. ACh, norepinephrine or epinephrine, 5-HT, adenosine, PGE, histamine, enkephalin, dopamine and ATP inhibit norepinephrine release through muscarinic, $\alpha_2$, 5-$HT_1$, $P_1$, EP, $H_2$, δ, $D_2$ and $P_2$ receptors respectively.

Whereas, epinephrine and angiotensin II activating $\beta_2$ and $AT_1$ receptors respectively release norepinephrine. Tyramine and amphetamine promote norepinephrine release. *Norepinephrine also exerts 'autoinhibitory feedback' mechanism in regulating its release from the adrenergic nerve terminals. Normally in the process of release of the transmitter, when depolarization reaches the nerve terminal the nerve membrane-bound adenyl cyclase is activated causing formation of cAMP from ATP. cAMP in turn helps in opening the Ca channels, resulting in free influx of Ca++ into the nerve terminal, faciitating fusion of membranes and exocytosis of norepinephrine (and ATP) from the vesicles. In the autoinhibitory feedback mechanism, the released norepinephrine activates the pre synaptic $\alpha_2$ receptors resulting in inhibition of adenyl cyclase, closing of Ca channels and the resultant failure of exocytois.*

**Adrenergic Receptors:** Are of two main types : α and β, which exist in different subtypes :

| Subtype | Location/Tissue | Effect | Agonists* | Antagonists* |
|---|---|---|---|---|
| $\alpha_1$ | Smooth muscles: Blood vessels and bronchi. | Constriction | Phenylephrine Methoxamine | Prazosin Doxazocin |
| | Smooth muscles: Bronchi, GI sphincters, uterus, bladder sphincter, seminal tract and iris-radial muscle. | Contraction | | |
| | Smooth muscles: GIT | Relaxation | | |
| | Liver | Glycogenolysis | | |
| | Salivary gland | K ion release | | |
| $\alpha_2$ | Smooth muscles: Blood vessels | Constriction/ Dilatation | Clonidine Clenbuterol | Yohimbine Idazoxan |
| | Smooth muscles: GIT | Relaxation | | |
| | B-islets of pancreas | Decrease insulin secretion | | |
| | Platelets | Aggregation | | |
| | Brainstem | Reduce sympathetic outflow | | |
| $\beta_1$ | Heart | Increase rate and force of contraction | Dobutamine Xamoterol | Atenolol Metoprolol |
| | Salivary gland | Amylase secretion | | |
| $\beta_2$ | Smooth muscles: Blood vessels and bronchi. | Dilatation | Salbutamol Terbutaline Salmeterol Formoterol | Butoxamine |
| | Smooth muscles: Bronchi, uterus, bladder detrusor, seminal tract and ciliary muscle. | Relaxation | | |
| | Smooth muscles: GIT | Relaxation | | |
| | Liver | Glycogenolysis | | |
| | Mast cells | Inhibition of histamine release | | |
| | Skeletal muscle | Contraction and Glycogenolysis | | |
| $\beta_3$ | Skeletal muscle | Thermogenesis | BRL 37344 | |
| | Fat Depots | Lipolysis and thermogenesis | | |

* Selective

Adrenoceptors are G-protein coupled-receptors: All activate Gs protein, except the α2 which activate Gi protein.

**Destruction and/or Dissipation of Action of NorA:** NorA (other catecholamines also) are enzymatically degraded by intracellular monoamine oxidase (MAO) and extracellular catechol-O-methyl transferase (COMT). MAO is a mitochondrial surface bound enzyme present in adrenergic nerve terminals, liver and intestinal epithelium. COMT is present in many neuronal and nonneuronal tissues. The end product of MAO oxidation of NorA is vanillylmandelic acid (VMA). Elevated urinary excretion of VMA is used in diagnosing

pheochromocytoma in man. It also oxidizes epinephrine, dopamine and 5-HT. MAO inhibition increases the stores of NorA or dopamine in adrenergic nerve terminals. MAO inhibitors exert anti-depressant effect.

The termination of transmitter action of NorA is mainly achieved by re uptake back into the presynaptic adrenergic terminal, from where it is released (uptake I) and partly through uptake into extraneuronal tissues (uptake II) and enzymatic breakdown by COMT. The re uptake replenishes the vesicular NorA stores in the nerve terminal. Reserpine makes more of NorA available for breakdown by MAO (see above) and ultimately depletes the vesicular stores of the transmitter. Tricyclic antidepressants like desipramine and cocaine or related local anaesthetics interfere with NorA uptake I causing enhanced peripheral (tachycardia, elevated BP etc) and central (euphoria and excitement) sympathetic effects. Most of the released/circulating epinephrine (from adrenal medulla) is removed through uptake II.

**Other Peripheral Mediators**

The other chemical mediators in nervous system and their effects include:

A. **Non-peptide Mediators:**
   a) **5-HT:** Intestinal neurons: Maintenance of GIT motility (peristalsis).
   b) **Histamine:** Vascular and nonvascular smooth muscles (relaxation and constriction, respectively), gastric parietal cells (gastric acid secretagogue), sensory nerve endings (nociception).
   c) **Dopamine:** In adrenergic neurons (renal vasodilatation and increased cardiac contractlity)
   d) **GABA:** In enteric neurons (inhibition of peristalsis).
   e) **NO:** In postganglionic parasympathetic neurons, vasodilatation in corpora cavernosa in penis (released from nitrergic nerves-diffusion into vascular smooth vessels in corpora cavernosa-activation of guanylate cyclase-cGMP-vasodilation-inactivation of cGMP by phosphodiesterase V. Phosphodiesterase inhibitor sildenafil prevents inactivation of cGMP prolonging vasodilatation in corpora cavernosa-penile erection).

B. **Peptide Mediators:**
   a) **Neuropeptide Y:** In postganglionic sympathetic nerve terminals (facilitation of vasoconstrictor effects of NorA.
   b) **VIP:** Vasoactive intestinal peptide: In parasympathetic postganglionic nerve endings (cotransmitter with ACh causing vasodilatation in salivary gland and increase in salivary secretion, bronchodilatation, and increase in motility of GIT
   c) **GnRH:** In enteric sympathetic ganglia: Cotransmitter with ACh, contributes to slow depolarization of postganglionic membrane.
   d) **Substance P:** In sympathetic ganglia and enteric neurons: Cotransmitter with ACh, contributes to slow depolarization. Released from afferent nociceptive sensory nerves, facilitates pain sensation (activation of nociceptive afferent fibres) promotes inflammation. Initially pain sensation was attributed to this peptide, hence named after **P**.
   e) **CGRPb** (Calcotonin gene-related peptide)**:** Along with substance P promotes neurogenic inflammation (pain, vasodilatation and vascular lekage).
   f) **Oipoid peptides:** Beta-endorphin, leucine-enkephalin and methionine-enkephalin and dynorphin. Formed and released from nerves in CNS and from nerves or other cells peripherally (during inflammation) and act like opium (morphine) analgesics.

COMT- catechol O- methyl transferase

# Chapter – 10: PHARMACOLOGY OF CHOLINERGIC SYSTEM

## 1. Parasympathomimetics

These drugs cause the effects similar to ACh or stimulation of post-ganglionic parasympathetic nerves or stimulation of cholinergic receptors (Cholinergics/cholinomimetics).

**Classification**: Based on mode of action into two major groups:

a. **Direct Acting (Cholinergic Agonists):** Produce effects through direct stimulation of cholinergic receptors, both muscarinic and nicotinic, more so on former; hence also generally called muscarinic agonis. Three categories:

i. **Choline Esters :** ACh, methacholine, bethanechol and carbachol (CCh) :
ii. **Cholinomimetic Alkaloids :** Pilocarpine (leaves of South American plant *Pilocarpus jobarandi*, or *P. microphyllus*), nicotine (leaves of *Nicotiana tabacum*), arecholine (Areca nut: *Areca catechu*) and muscarine (mushroom *Amanita muscaria*)
iii. **Synthetic Analogues of Cholinomimetic Alkaloids:** Aceclidine, oxotremorine and McNA-343

**Relative Specificity of muscarinic agonists**

| Cholinergic Agonist | Receptor Affinity | | Breakdown by AChE |
|---|---|---|---|
| | Muscarinic | Nicotinic | |
| Acetylcholine | +++ | +++ | ++++ |
| Bethanechol | +++ | – | – |
| Carbachol | ++ | +++ | – |
| McNA-343 | ++ | – | – |
| Methacholine | +++ | + | ++ |
| Muscarine | +++ | – | – |
| Oxotremorine | ++ | – | – |
| Pilocarpine | ++ | – | – |

* Carbachol is long acting highly potent cholinergic drug resistant to AChE. It is a carbamate ester; presence of carbamate moiety provides steric hindrance to breakdown by the enzyme.

b. **Indirect Acting (Anticholinesterases, AntiChEs):** Cause accumulation of ACh by inhibiting the enzyme AChE. Three types based on duration/nature of inhibition:
   i. **Reversible AntiChEs**: Based on duration of inhibition
      1. **Short Acting:** Edrophonium
      2. **Intermediate Acting:** Neostigmine, physostigmine, pyridostigmine and carbamate insecticides (carbaryl, carbofuran, benfuracarb etc)
      Physostigmine is an alkaloid obtained from the dried ripe seeds of *Physostigma venenosum* an African woody climber (Calabar bean or ordeal bean).
   ii. **Irreversible AntiChEs (Long Acting AntiChEs)**: Ecothiophate, dyflos (DFP) and OP insecticides (Parathion, malathion etc)

**Pharmacological Effects of Acetylcholine:** ACh is primarily used in experimental pharmacology where it is injected intravenously.

**A. Muscarinic Effects:**

1. **Effect on Heart:** Decreases heart rate (depression of SA node), force of contraction (increase in duration of conduction velocity in atria and depression of A-V conduction) and cardiac out put.
2. **Effect on smooth muscles of Blood Vessels:** Relaxation of vascular smooth muscle and dilatation of blood vessels causing fall in BP (generalized vasodilatation).
3. **Effect on nonvascular smooth muscles: Contraction:** Increase in tone and motility (peristalsis) of GIT, constriction of bronchi (apnoea), contraction of uterus and contraction of gall or urinary bladder.

**Contraction** of detrussor trigonale, while the sphincter of urinary bladder is relaxed leading voiding of bladder,

4. **Effect on Exocrine Glands:** Increase in gastric, intestinal, pancreatic, salivary, bronchial, nasopharyngeal and lacrimal secretions and sweating.
5. **Effect on Eye:** Parasympathetic system accommodates the eye for near vision and regulates intraocular pressure. ACh constricts sphincter pupillae causing miosis and reduces intraocular pressure (promoting drainage of ocular fluid through the canal of Schlemm). ACh causes contraction of ciliary muscle resulting in relaxation of suspensory ligament of lens, adjusting for near vision (spasm of accommodation). ACh on topical application has no effect on eye (not absorbed).
6. **Male Sex Organ:** Erection due to vasodilatation and increased blood flow.

(The major effects of muscarinic effects of ACh are referred as SLUD: Salivation, lactrimation, urination and defecation)

B. **Nicotinic Effects:**

1. **Effect at Autonomic Ganglia:** ACh in higher doses stimulates both sympathetic and parasympathetic ganglionic transmission. In atropinized animals high doses of ACh causes tachycardia and increase in BP.
2. **Effect on Adrenal Medulla:** Stimulates (in large doses) epinephrine secretion from adrenal medulla.
3. **Effect at Neuromuscular Junction:** Contraction of skeletal muscles through activation of nicotinic receptors. Excess concentration causes persistent depolarization of muscle fibres (motor end plate) and thus paralysis of skeletal muscles. Edophonium can be used to reverse neuromuscular blockade of curariform drugs.

C. **CNS Effects:** Muscarinic agonists which can pass through the blood brain barrier (BBB) cause muscular tremor/fasciculations, hypothermia and increased locomotor activity (activation of M1 receptors). ACh, following IV injection, being a quarternary ammonium compound does not cross the BBB and hence has no central effects. .

The other cholinergic agonists produce effects generally line with that of ACh or parasympathetic stimulation, but the intesnsity of which vary depending upon their relative receptor affinity. Among the other choline esters carbachol is more potent than methacholine or bethanechol (see the Table above for relative receptor specificity). The muscarinic effects of carbachol are not adequately blocked by muscarinic antagonist atropine. The choline esters are effective after oral administration, except the ACh. The IVly injected ACh is rapidly inactivated by BChE (plasma) and AChE.

**Therapeutic Uses of Muscarinic Agonsists:**

a) Glaucoma: **Pilocarpine** (Pilocarpine nitrate as 0.5-2 % eye drops) is the most effective (readily absorbed through conjunctival membrane being a tertiary amine and action lasts for about 24 hr).
b) **Carbachol** is used in colic and intestinal impaction in horse; in correcting ruminal atony and impaction in ruminiants (1-2 mg SC, repeat at one hr intervals) and as an oxytocic during mid farrowing to reduce stillbirths in Sow (2 mg SC single dose). Not generally preferred due to potent muscarinic actions, over dosage can cause overstimulation and ruputure of GIT or uterus; cannot be antagonized by atropine).
c) **Bethanechol** can be in atony of GIT or urinary bladder.

**Anticholinesterases (AntiChEs):**

ACh is enzymatically broken down by the cholinesterases. ACh interacts with both anionic and esteratic sites of ChE (substrate-enzyme complex), the enzyme is acetylated cleaving choline from ACh molecule and immediately the acetyl group from the acetylatedChE is spontaneously separated regenerating active ChE. All the reactions proceed in forward direction at a very rapid rate (microseconds)

ACh + ChE → ACh-ChE complex → Choline + Acetylated ChE → Acetate + Regenerated ChE

The reversible antiChE carbamates (like neostigmine, physostigmine, pyridostigmine, ambenonium and edrophonium) also react with both the sites of ChE forming carbamylatedChE. Regeneration of active ChE from carbamylation is not spontaneous, but a slow process taking several minutes.

Neostigmine + ChE → Neostigmine-ChE complex → CarbamoylatedChE + 3-hydroxyphenyl trimethyl ammonium → Dimethylcarbamic acid + Regenerated ChE

The irreversible antiChE organic phosphates (like DFP, TEPP, ecothiophate) or OP insecticides (parathion, malathion etc) interact with the esteratic site of ChE forming phosphorylatedChE. Regeneration of active ChE from phosphorylation takes a long time. New synthesis, extending over several weeks restores the enzyme activity very slowly.

DFP + ChE → DFP-ChE complex → HF + PhosphorylatedChE → Diisopropylphosphoric acid + Regenerated ChE

The antiChEs produce pharmacological effects identical to parasympathomimetics or cholinergic effects. The irreversible antiChE OP compounds are of toxicological concern in man and animals (indiscriminate use as insecticides). In therapeutic management of OP insecticide toxicity, the muscarinic toxic manifestations can be counteracted by muscarinic antagonist atropine. In addition, regeneration of active ChE from stable phosphorylation can be achieved by administration of ChE reactivating oximes like pralidoxime (See for detailed account in Toxicology).

PhosphorylatedChE + Pralidoxime → Phosphonate-NOH (of pralidoxime) + Active ChE

Distigmine and pyridostigmine (longer duration of action, but less potent than neostigmine) are structural analogues of neostigmine. Ambenonium is a synthetic potent AChE inhibitor (having sustained action than neostigmine). Demecarium, a reversible antiChE (inhibits more of AChE than BChE), is made up of combination of two neostigmine molecules.

**Therapeutic Uses of AntiChEs:**

1. Neostigmine (15 to 30 mg orally, 0.5 to 2 mg SC or IM) in reversing the skeletal muscle paralysis by non-depolarizing neuromuscular blockers.
2. Neostigmine or pyridostigmine (60 to 240 mg orally or 1 to 5 mg SC or IM) in treating myasthenia gravis in man.
3. Edrophonium to detect myasthenic crisis in man.
4. Ecothiophate and physostigmine (physostigmine salicylate as 0.25 to 0.50% aqueous solution) at as eye drops in treating glaucoma in man.
5. Physostigmine (2 to 4 mg SC or IV) as antidote for over dosage of phenothiazines and tricyclic antidepressants.
6. Neostigmine or edrophonium (0.25 mg/kg, IV after atropine @ 50 microgram/kg to block muscarinic actions) along with antisnake venom in treating cobra snake bite (cobra venom contains neurotoxins α-bungarotoxin and β-bungarotoxin, which cause muscle paralysis respectively, by blocking nACh receptors at the motor end plate and preventing ACh release from the motor nerve terminal ( both the toxins exert interfere with neuromuscular transmission).
7. OP insecticides as insecticides in plant protection and as ectoparasiticides and anthelmintics in veterinary medicine.

## 2. Parasympatholytics

These drugs prevent the effects of stimulation of parasympathetic post-ganglionic nerves and/or the effects of ACh or cholinergic drugs, mainly the muscarinic actions (Cholinergic blockers; primarily the Muscarinic Blockers/Antagonists or Antimuscarinic Drugs, Cholinolytics or Anticholinergics).

**Classification:**

**Based on Source:**

i. **Natural Alkaloids:**
   a. Atropine: The main alkaloid of *Atropa belladonna* (Deadly nightshade) or *A. accuminata*
   b. Hyoscine: The main alkaloid of *Datura stramonium* (Thorn apple) or *D. alba, Scopolia carniolica* or *Hyoscyamus niger*

ii. **Synthetic/Semisynthetic Compounds (Atropine Substitutes):** Homatropine, eucatropine, ipratropium, cyclopentolate, tropicamide, pirenzepine, glycopyrrolate, methantheline, propantheline, oxyphenonium, dicyclomine, flavoxate, oxybutynine, glycopyrrolate and tolterodine.

**Based on Chemistry:**

i. **Teritiary Amines**: Atropine, benzatropine, oxybutyrin, dicyclomine, scopolamine and trihexyphenidyl.

ii. **Quarternary Amines**: Glycopyrrolate, ipratropium and propantheline

**Mechanism of Action:** Muscarinic antagonists, the prototype being atropine, act as competitive antagonists of ACh on muscarinic receptors.

**Pharmacological Effects of Muscarinic Antagonists**: All the drugs produce in general similar effects, with variations in selectivity.

A. **Secretions:** Inhibition of secretion of exocrine glands (salivary, gastric acid, lacrimal, nasopharyngeal, bronchial and sweat glands).
B. **Eye:** Mydriasis by relaxation of smooth muscles of sphincter of iris. Paralyss of ciliary smooth muscle causing loss of accommodation for near vision (cycloplegia). Rise in intraocular pressure (glaucoma). The mydriatic and cycloplegic effects of atropine may persist for more than a week.
C. **Smooth muscles of GI Tract:** Antispasmodic, reduction in tone and motility. Atropine abolishes intestinal spasmogenic action of cholinergics and morphine.
D. **Smooth muscles of other organs:** Relaxation of gall bladder and bile ducts, relaxation of urinary bladder and increase tone of trigonal sphincter (urinary retention), relaxation of bronchi and no significant effect on uterus.
E. **Heart:** Atropine at low doses decreases heart rate (due to blockade of muscarinic autoreceptors on vagal nerve endings augmenting ACh release: partial agonist), followed by increase in heart rate due to blockade of cardiac muscarinic ($M_2$) receptors and rise in BP due to stimulation of vasomotor centre. Rapid IV injection causes sudden fall in BP.
F. **CNS:** Atropine causes slight excitation in therapeutic doses (blockade of muscarinic receptors in CNS). Physostigmine reverses the blockade (antidote to atropine/belladonna poisoning). Hyoscine causes mild sedation in low doses and excitement in high doses. It also has antiemetic effect (can be used in motion sickness).
G. **Skin:** Anhydrotic in man and cats (cholinergic), but not in horses (adrenergic).

**Therapeutic Uses of Atropine/Antimuscarinic Drugs:**

1. Atropine as preanesthetic (reduction in bronchial and salivary secretions) @ 0.02 – 0.1 mg/kg IV, IM or SC in different species.
2. Atropine as antidote to antiChE insecticide poisoning @ 0.2 – 0.5 mg/kg, one-fourth the dose IV and the rest IM in different species.
3. Atropine for relief of heaves in horses @ 30 mg SC (total dose).
4. Homatropine: 1-2% solution as mydriatic for opthalmological exam (preferred to atropine because of short duration effect as compared to atropine which causes persistent mydriasis and cycloplegia). Cyclopentolate and tropicamide are also the ophthalmic antimuscarinic drugs.
5. Glycopyrrolate as preanaesthetic to prevent salivation and reflex vagal stimulation of heart @ 0.01 mg/kg SC, IM or IV. It is also used as GI antispasmodic.

6. Atropine or its synthetic analogogues is also used as smooth muscle spasmolytic (GIT, uterus, bladder, ureter, bile duct and bronchioles), in peptic ulcer, Parkinsonism and urinary incontinence; and hyoscine in motion sickness in man. Atropine is the preferred drug in cholinergic bronchospasm. Dicyclomine and propantheline can be used as GI and genitourinary antispasmodics. Oxybutyrin has antispasmodic and local anaesthetic activity.

## A. Ganglionic Transmission

The main pathway of impulse transmission through the ganglia involves release of ACh from preganglionic nerve terminals and activation of post-junctional nicotinic receptors causing depolarization (EPSP) of the post-junctional membrane in ganglia and propagation of the impulse through post-ganglionic nerve. Drugs alter autonomic ganglionic function either stimulating transmission (ganglionic stimulants) or inhibiting ganglionic transmission (ganglionic blockers):

### 3. Ganglionic Stimulants

**Classification**: Based on origin:

**A. Natural Alkaloids**: Nicotine (from leaves of *Nicotiana tabacum*) and Lobeline (leaves of *Lobelia inflata*)

**B. Synthetics**: DMPP (dimethylphenylpiperazinium, selective on ganglionic nicotinic receptors), tetramethyl ammonium (TMA) and epibatidine.

The initial stimulant effect of nicotine is followed by persistent depolarization of post-junctional membrane and blockade of ganglionic transmission. Both DMPP and TMA do not possess this action. The ganglionic stimulants are used as experimental pharmacological tools.

**Pharmacological Effects:** The effects of ganglionic stimulants depend upon the prevailing sympathetic or parasympathetic tone at the ganglia.

**a) Effect on CNS**: Excitement. Large doses cause tremors or convulsions. Stimulation of medullary respiratory centre and activation of carotid and aortic body chemoreceptors. Excitement is followed by depression of CNS.

**b) Effect on CVS**: Increase in heart rate and BP due to stimulation of sympathetic ganglia and release of epinephrine from adrenal medulla. Chemoreceptor activation also contributes to increase in heart rate, vasoconstriction and hypertension.

**c) Effect on GIT**: Salivation, increase in tone and motility and defecation (parasympathetic).

**Nicotine Toxicity**: Acute toxicity is characterized by CNS excitation, tremors, convulsions, salivation, nausea, vomiting, diarrhoea and tachycardia. CNS excitation is followed by severe depression. Death results from respiratory failure (central and peripheral actions). Treatment consists of administration of analeptics and removal of unabsorbed nicotine from the GIT.

### 4. Ganglionic Blockers

**Classification**: Based on mechanism of action:

**a) Receptor Antagonists**: Interfere with post-synaptic action of ACh. Competitive antagonists of ACh for nicotinic receptors in autonomic ganglia. The drugs are:

| | | |
|---|---|---|
| Hexamoethonium | Mecamylamine | Tetraethylammmonium (TEA) |
| Pentolinium | Trimethaphan | |

**b) Prolonged Depolarization**: Nicotine: Initial stimulation followed by persistent depolarization. Irreversible antiChEs also cause prolonged depolarization (excess of ACh).

**Pharmacological Effects**: Ganglionic blockers block transmission indiscriminately in both sympathetic and parasympathetic ganglia. Therefore the effects are related to the nature of existing predominant tone on the effector system.

**a) Effect on CVS**: Blockade of vascular sympathetic tone causing vasodilatation, increased peripheral blood flow, venous pooling, decreased cardiac out put, hypotension. and reflex tachcardia.
**b) Effect on GIT**: Blockade of parasympathetic tone causing reduced tone and motility (constipation).
**c) Eye**: Blockade of parasympathetic tone causing mydriasis and cycloplegia.
**d) Effect on Bladder**: Blockade of parasympathetic tone causing relaxation of bladder, constriction of sphincter and urinary retention.
**e) Effect on Skin**: Blockade of sympathetic tone causing anhydrosis.
**f) Salivary Glands**: Blockade of parasympathetic tone causing xerostomia.

The ganglionic blockers are used in experimental pharmacology and are of some value (trimetaphan) in treating hypertension in man (not usually preferred due to many side effects due to indiscriminate ganglionic blockade).

### 5. Neurmuscular Transmission

The function of skeletal muscles is regulated by the somatic (cholinergic) motor nerves The junction between the motor nerve ending and the skeletal muscle fibre is called the neuromuscular junction. Blocking neuromuscular transmission has clinical application. The drugs which interfere with transmission at neuromuscular junction are called neuromuscular blockers (NMBs). The pharmacology of neuromuscular transmission and NMBs are described in 'Neuropharmacology'.

# Chapter – 11: PHARMACOLOGY OF NORADRENERGIC TRANSMISSION

The drugs modulating the adrenergic transmission include:

## 1. Sympathomimetics

These drugs produce effects similar to stimulation of sympathetic post-ganglionic nerves and/or the effects of NorA or epinephrine (Adrenergics/noradrenergics).

**Classification:**

**A. Basing on Mode of Action:**

a. **Direct Acting:** By direct activation of adrenoceptors : Adrenoceptor Agonists:
   - i. **α and β Agonists:** Epinephrine and Norepinephrine
   - ii. **α agonists:** Methoxamine
   - iii. **β Agonists:** Isoprenaline (isoproterenol)
   - iv. **$\alpha_1$ Agonists:** Phenylephrine
   - v. **$\alpha_2$ Agonists:** Clonidine, guanafacine, guanabenz and clenbuterol
   - vi. **$\beta_1$ Agonists:** Dobutaime and xamoterol
   - vii. **$\beta_2$ Agonists:** Salbutamol, salmeterol, fomterol and terbutaline

b. **Indirect Acting:** By promoting release of NorA from post-ganglionic sympathetic nerve terminals: Tyramine, amphetamine and ephedrine. These drugs have a very weak action on adrenoceptors. Due to their structural similarity to NorA, the indirectly acting adrenergic drugs are transported into the adrenergic nerve terminal by the vesicular monoamine transporter (VMAT), located in the nerve membrane, which carries NorA during up take I (reuptake). After entering the cytosol of the neuron, these drugs are again transported into the vesicle by the vesicular membrane VMAT in exchange of NorA (displace the NorA present in the vesicle) and which is released from the nerve terminal. Amphetamine also lowers the re up take of NorA (up take I) and increasing its action on the effectors.

**B. Basing on Chemical Structure:**

- i. **Catecholamines**: Amine drugs with catechol nucleus (benzene ring with two OH groups: Epinephrine, NorA, Dopamine and Isoprenaline
- ii. **Non-Catecholamines**: Drugs without catechol nucleus: Phenylephrine, tyramine, metaraminol, amphetamine etc.

**Important Features of Structure Activity Relationship:** The receptor specificity and sensitivity to enzymic breakdown of adrenoceptors are related to their chemical structure as illustrated below:

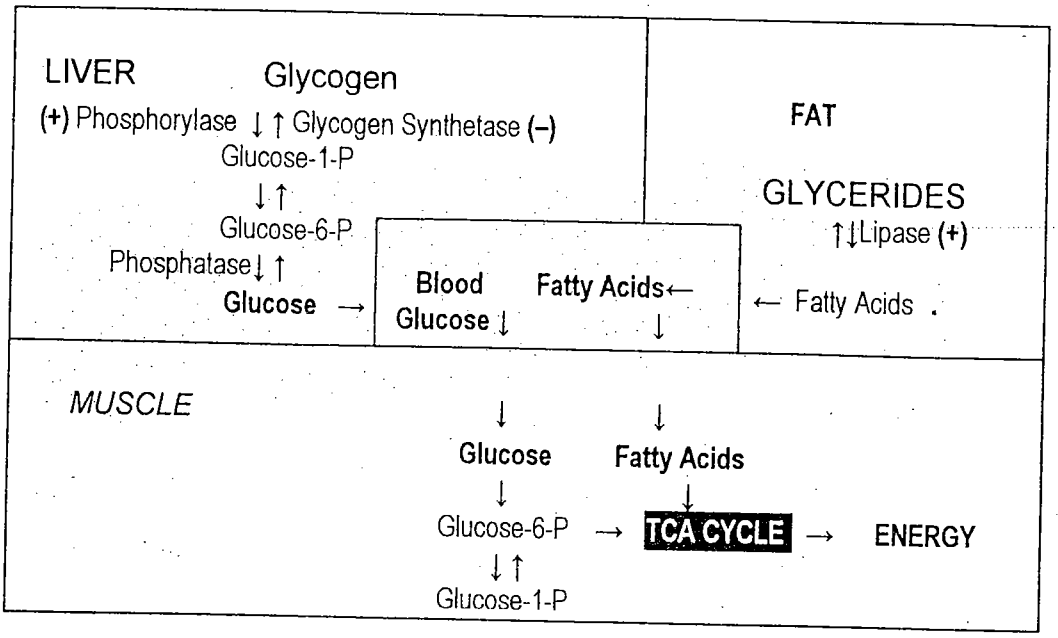
a) β-phenylethylamine (BPEA), the parent compound of adrenoceptor agonists (catecholamines) lacks agonistic action on adrenoceptors.
b) Addition of OH group at position 3 and 4 in benzene ring of BPEA yields catecholamines having alpha and beta activities; when one or both –OH groups are absent the potency declines..
c) Increase in bulkiness of substitutions at N increases beta potency :
   - i. Substitution of $CH_3$ group at N yields beta activity (Epinephrine).
   - ii. Substitution of $CH(CH_3)_2$ at N yields isoprenaline with beta activity only(Isoproterinol, salbutamol).
d) Substitution at alpha C atom blocks oxidative inactivation by MAO (ephedrine and amphetamine).
e) Substitution of OH in side chain at beta C atom increases alpha activity (norepinephrine).
f) Removal of one or both OH groups in benzene ring (Tyramine, ephedrine and amphetamine: indirect acting) results in very weak affinity to adrenoceptors and confers central stimulant action (increase in lipid solubility).
g) Substitution of Cl groups in place of OH groups (benzene ring) in isoprenaline (isoproterinol) results in dichloroisoproterinol with beta antagonism.

**Pharmacological Actions of Sympathomimetics:** Generally the effects are opposite to those of cholinergics (muscarinic agonists): **Prototype: Epinephrine:**

a) **Effect on Heart: Cardio-excitatory:** Increase rate and force of contraction of myocardium and cardiac output. Increase oxygen consumption and lower myocardial efficiency.
b) **Effect on Smooth Muscles:** The effects vary from organ to organ:
   i) **Blood Vessels:** Strong contraction in skin, splanchnic vascular beds and mucous membranes, dilation in skeletal muscles and mesentery (predominance of $\beta_2$ receptors) and constriction of arterioles as well as large veins and arteries. The net result is increased peripheral resistance contributing to rise in systolic and diastolic arterial pressure. Cerebral, coronary and pulmonary vessels are not affected.
   ii) **Effect on BP:** Rapid IV injection of adrenaline causes marked rise in ean BP (α -mediated vasoconstriction) and direct beta-mediated cardiac stimulation. The rise in BP is followed by a momentary fall in BP (reflex vagal action), this is called biphasic action of adrenaline. A very small dose of adrenaline (0.01 microgram/kg) causes a sharp, but transient fall in BP, as compared to the biphasic action of normal dose (1 microgram/kg), this is due to activation of β -receptors in blood vessels, which are more sensitive to the action of adrenaline. Adrenaline injection after α-blockade results in fall in BP (Dale's vasomotor reversal: see below). Norepinephrine causes only rise in BP due α-mediated action (Dale's vasomomotor reversal is not observed: no activation of β-two receptors). Isoprenaline causes only fall in BP (β -two action). The $\alpha_2$ agonists mediate reduction in central sympathetic ouflow causing reduced peripheral adrenergic activity (decreasing BP).
   iii) **Respiratory Syetem:** Relaxation of bronchi (β-two).
   iv) **Uterus:** Varies according to species, pregnancy and oestrus cycle. Rat uterus is relaxed. Rabbit uterus is contracted. Contraction of non-pregnant and relaxation during last month of pregnancy of human uterus.
   v) **GI:** Reduced tone and motility due to relaxation of GI smooth muscles and constriction of sphincters (α and β). The relaxant effect in part is also due to stimulation of pre synaptic $\alpha_2$ receptors inhibiting release of ACh from cholinergic nerve terminals in GIT.
   vi) **Bladder:** Relaxation of detrusor and contraction of trigone sphincter (inhibition of micturition)
   vii) **Others:** Contraction of splenic capsule and release of RBC into circulation. Contraction of pilomotor muscle of hair follicles

c) **Effect on Eye:** Mydriasis due to contraction of radial muscle of iris (α). Relaxation of ciliary muscle. Decrease in intraocular pressure.
d) **Effect on Skeletal Muscle:** Increase rate and force of contraction of skeletal muscles ($\beta_2$) contributing to thermogenesis. Abuse of clenbuterol (anabolic $\beta_2$ agonist) as performance enhancer by athletes. Neuromuscular transmission is facilitated as activation of α-receptors at motor nerve endings promote ACh release
e) **Effect on CNS:** Injected catecholamines have no effect, as they do not cross blood brain barrier. Stimulation especially by amphetamines causing wakefulness, increased respiration and psychomotor activity in man. Amphetamines also have anorectic effect. Direct stimulation of respiratory centre.
f) **Metabolic Effects:** Epinephrine has a significant role in energy metabolism. It causes hyperglycaemia(β-two), hyperlipaemia (Lipolysis: (β-three) , hyperlacticidaemia, hypokalaemia and inhibition of insulin release (α-two) and increase in glucagons secretion (α and β-two)
g) **Miscellaneous Effects:** Inhibition of histamine release from mast cells in anaphylaxis and allergy, lymphocyte proliferation and cytokine production ($\beta_2$), and platelet aggregation, acceleration of blood clotting, leucocytosis and eosinopenia by epinephrine,

**Regulation of Energy Metabolism by Epinephrine (Adrenaline)**




**Clinical Uses of Sympathomimetics**

a. Epinephrine in prolonging local anaesthesia (at a concentration of 1: 100000 to 1 in 20000): Increases duration of anaesthsia by decreasing absorption of the local anaesthetic (local vasoconstriction in the area).
b. Epinephrine as local hemostatic: Application of gauze moistened with epinephrine (1: 1,00,000 – 1: 20,000 solution): Arrests bleeding by intense local vasoconstriction and promoting clotting.
c. In allergic/anaphylactic shock to counter acute hypersensitivity reactions: Epinephrine to reverse acute hypotension and bronchial constriction (life saving): Cattle & Horse: 4-8 ml of 1:1000 dilution IM or SC; Sheep & Swine: 1-3 ml of 1:1000 solution IM or SC; Dog & Cat: 1-5 ml of 1:10,000 dilution IM or SC.
d. As cardiac stimulant to reverse cardiac arrest:
   i) Epinephrine 0.5 – 1 ml of 1:10,000 dilution directly into ventricles.
   ii) To reverse AB block: Isoprenaline 3 – 5 microgram/kg by slow IV injection
e. To prevent threatened abortion: Salbutamol
f. To relieve acute asthmatic attacks: As bronchodilators (Salbutamol, terbutaline or fomoterol).
g. As nasal decongestant: Oxymetzoline or ephedrine

**2. Sympatholytics**

Are drugs which prevent the effects of stimulation of post-ganglionic sympathetic nerves or those of sympathomimetics, adrenergics or catecholamines (Adrenergic Blockers).

**Classification: Based on Mode of Action:**

**A. Direct Acting: Adrenoceptor Blockers or Antagonists:**

**i) α Receptor Blockers**

a) **Non-Selective α blockers:** Phenoxybenzamine, phentolamins, tolazoline, ergotamine and ergotoxine.
b) **Selective $\alpha_1$ blockers:** Prazosin, doxazosin and terazosin
c) **Selective $\alpha_2$ blockers:** Yohimbine (alkaloid of Yohimbee tree)
Phenoxybenzamine has long lasting blocking action as it covalently binds to the α receptors and also antgonizes Ach, histamine and 5-HT.

**ii) β Receptor Blockers:**

a) **Non-Selective β blockers:** Propranolol, sotalol, nadolol, timilol and alprenolol
b) **Selective $\beta_1$ Blockers:** Atenolol, metoprolol, acebutolol and esmolol
c) **Selective $\beta_2$ Blockers:** Butoxamine (also weak α agonist)

**iii) Both α and β receptors (Mixed blockers):** Medroxolol, Labetalol and carvedilol. Labetalol is also a partial agonist on $\beta_2$

**Pharmacological Effects of Adrenoceptor Blockade/Antagonism:**

a) **α Receptor Blockade: Significant effect on CVS.** Peripheral α1 blockade results in vasodilatation and hypotension. Central α2 antagonism results in increase in central sympathetic out flow causing increased smpathetic effect peripherally leading to hypertension (increase in peripheral vasoconsstriction). The α2 blockade also increases insulin secretion. Following α1 blocker administration epinephrine causes only fall in BP due to activation of β receptors causing vasodilatation. This phenomenon is called as epinephrine reversal, pressor reversal of epinephrine or Dale's reversal or Dale's vasomotor reversal. α-blockade does not interfere with β-mediated effects of adrenergic drugs.

b) **β Receptor Blockade:** Reduction in force and rate of contraction of heart and cardiac out put, potentiation of pressor effect of epinephrine and antagonism of vasodilatation and hypotension of isoprenaline. Propranolol blocks β-mediated of adrenergic drugs on respiratory tract, lipolysis, uterine relaxation etc. $\beta_1$ antagonists decrease rennin and thus reduce the formation of angiotensin II. The beta blockers (propranolol, timolol, bataxolol, labetalol and pindolol) also have quinidine-like (antiarrhythmic) activity.

**Clinical Uses of Adrenoceptor Antagonists:** These have a wide range of clinical uses in human medicine.

a. Phenoxybenzamine and phentolamine in treatment and diagnosis of phaeochromocytoma respectively.
b. Prazosin in hypertension.
c. Tamsulosin in prostatic hyperplasia.
d. Propronolol, metoprolol, practolol and alprenol in angina, hypertension, cardiac arrhythmia, anxiety tremor and glaucoma.
e. Labetalol in hypertensive crisis (pregnancy, cheese reaction).
f. Carvedilol in CHF (antagonize sympathetic overactivity on myocardium).
g. **Propranolol is used to treat ventricular fibrillation in dog (1 mg/kg IV).**

**B. Indirect Acting: Also called as Anti-Adrenergic Drugs or Adrenergic Neuron Blockers:** Act by interfering with neurotransmitter function of adrenergic nerves, but not act (block or anatonize) on the adrenoceptors.

**Classification:** Based on mode of action:

**a) Interfering with synthesis of Norepinephrine**

**i) Inhibition of tyrosine hydroxylase:** α-methyl-p-tyrosine (metyrosine): Formation of DOPA and subsequent is blocked.

**ii) Inhibition of DOPA decarboxylase:** Carbidopa: Formation of dopamine is blocked.

**iii) Formation of false transmitter:** α-methyldopa: The drug is processed by dopa decarboxylase to α-methyldopamine, which in turn by dopamine hydroxylase to finally form α-methyl norepinephrine, which does not possess the transmitter function of norepinephrine. It replaces norepinephrine in synaptic vesicles and is relesed from the sympathetic nerve terminals.

**b) Interfering with storage of Norepineprine:** Reserpine (alkaloid of roots of *Rauwolfia serpentina*); prevents transport of axoplasmic norepinephrine (which is taken back into the nerve terminal through re uptake) into the vesicles by binding to the norepinephrine carrier protein. Norepinephrine remains in the cytosol, where it is oxidized by $MAO_A$, ultimately, the vesicular stores of norepinephrine are depleted (reserpine interferes with salvage of norepinephrine into the vesicles).

**c) Interfering with release of Norepinephrine:** Guanethidine and betanidone inhibit re uptake process by binding to the norepinephrine carrier protein; instead of norepinephrine these drugs are carried into the nerve terminal. Similarly in the nerve terminal they also bind to the carrier protein and are transported into the synaptic vesicles in the nerve terminal (concentrated in nerve terminal and

vesicles); thus depleting vesicular norepinephrine stores. These drugs also interfere with norepinephrine release, by local anaesthetic action.

**d) Interfering with Norepinephrine re uptake:** Cocaine and imipramine prevent norepinephrine re uptake into the nerve terminal.

Uses of Adrenergic Neuron Blockers: As antihypertensives (in man).

EXERCISE

1) Describe how the impulses are conveyed through the nerves.
2) Describe impulse conduction and transmission with suitable illustrations.
3) What is cholinergic transmission? Indicate its sites/locations. Descibe the synthesis, storage, release and breakdown of ACh.
4) What is adrenergic transmission? Descibe the synthesis, storage, release and breakdown of adrenaline and noradrenaline.
5) What are cholinergic receptors? Describe the types, location and associated effects. Indicate the agonists and antagonists of cholinergic receptors.
6) What are adrenoceptors? Describe their types, location and associated effects. Indicate the agonists and antagonists of adrenoceptors.
7) What are cholinomimetics? Give their classification based on mode of action. Describe the pharmacological effects of parasympathomimetics.
8) What are adrenergic drugs? Give their classification based on mode of action. Describe the pharmacological effects of sympathomimetics.
9) What are muscarninc blockers? Descibe the pharmacological effects of muscarinic blockade? Give the clinical indications of cholinergic blockers.
10) What are adrenoceptor blockers? Give their classification. Describe the pharmacological effects of adrenoceptor blockade.
11) What are antiadrenergic drugs? Give their classification and describe how adrenergic neuron function is interfered.
12) Describe the interaction of ACh with cholinergic receptors and the associated transduction mechanisms involved in producing the cellular effects.
13) Describe the interaction of NorA with adrenoceptors and the associated transduction mechanisms involved in producing the cellular effects.
14) What are the metabolic effects of adrenaline? Describe the receptor ineraction and the transduction mechanisms in regulating glucose metabolism.
15) **Write a short note on the following**:
    a. Impulse conduction
    b. Impulse transmission
    c. Nerve action potential
    d. Synthesis of acetylcholine
    e. Synthesis of adrenaline
    f. Cholinergic receptors
    g. Adrenoceptors
    h. Cholinesterases
    i. Enzymatic breakdown of adrenaline
    j. Anticholinesterases
    k. Antiadrenergic drugs
    l. Choline esters
    m. Catecholamines
    n. Biphasic response of adrenaline
    o. SAR of catecholamines
    p. Metabolic effects of adrenaline
    q. Adenyl cyclase-cAMP system
    r. Indirecly acing adrenergic drugs
    s. False transmitter formation
    t. Epinephrine reversal
    u. Pressor reversal
    v. Nicotinic action of acetyl choline
    w. Tachyphylaxis
    x. Ganglionic blockers
    y. Release and uptake of NorA
    z. Muscarinic blockers
    aa. Nicotinic blockers
17. **Differentiate between the following pairs**:
    b. Impulse conduction & Transmission
    c. Tetradotoxin & Batrachotoxin
    d. AChE & BChE
    e. Alpha & Beta receptors
    f. Nicotinic & Muscarinic receptors
    g. Cholinergic agonists & AntiChEs
    h. Organic Phosphates & Carbamates
    i. Atropine & Homatropine
    j. Adrenaline & Noradrenaline
    k. Dopa & Alpha-methldopa
    l. Reserpine & Cocaine
    m. EPSP & IPSP
    n. Saxitoxin & local anaesthetics
    o. DFP & Physostigmine
    p. Tyramine & Metyramine
    q. Nicotine & Trimethaphan
    r. Ephedrine & Guanethidine
    s. Choline & Hemcholinium
    t. Vesimicol & Hemicholinium
    u. $M_2$ and $M_3$ receptors

v. $\beta_1$ and $\beta_2$ receptors
w. MAO & COMT
x. ACh and Carbachol
bb. Phosphorylated AChE & Acetylated AChE
cc. Depolarization & Hyperpolarization
dd. Pentamethonium & Decamethonium
ee. α-Bungarotoxn and β-Bungarotoxin
ff. Atropine mydriasis & Adrenaline mydriasis
kk. Tetradotoxin and Batrachotoxin
y. Muscarine & Nicotine
z. Adrenaline & Amphetamine
aa. Edrophonium & Pralidoxime
gg. Central $\alpha_2$ and peripheral $\alpha_2$ receptors
hh. Phosphorylated AChE & Acetylated AChE
ii. Isoproterenol & Dichloroisoproterenol
jj. Sympathetic system & Parasympathetic system
ll. Somatic nerves & Autonomic nerves

18. **Describe mechanism of action of the following:**
a. Adrenaline
b. Acetylcholine
c. Methyldopa
d. Guanethidine
e. Reserpine
f. Hexamethonium
g. Physostigmine
h. Neostigmine
i. Ephedrine
j. Tyramine
k. Metyrosine
l. DFP
m. Vesamicol
n. Ciguatoxin
o. Hemicholinium
p. Atropine
q. Yohimbine
r. Butoxamine
s. Nicotine
t. Muscarine
u. Arecoline
v. Hyoscine
w. Glycopyrrolate
x. Phenoxybenzamin
y. Propranolol
z. Imipramine
aa. Bungarotoxins
bb. Black widow spider toxin
cc. Tetrodotoxin
dd. Botulinum toxin
ee. Batrachotoxin
ff. Saxitoxin

19. **Explain the following with suitable illustrations:**
a. Dales reversal
b. Nicotinic action of ACh
c. Tachyphylaxis
d. False transmitter
e. Impulse transmission involves release of transmitter at presynaptic terminals
f. Irreversible AChE inhibition
g. SAR of catcholamines
h. Nerve action potential
i. Reactivation of phosphorylated AChE

20. **What do you mean by the following? Answer in one or wo sentences for each:**
a. Nerve action potential
b. Depolarization
c. Hyperpolarization
d. Adrenoceptors
e. Cholinoceptors
f. EPSP
g. IPSP
h. False transmitter
i. Dale's reversal
j. AChE
k. BuChE
l. True ChE
m. Pseudo ChE
n. COMT
o. MAO
p. Nicotinic action on ganglia
q. Synapse
r. Conduction
s. Transmission
t. Neurohumoral transmitter
u. Catecholamine
v. Synaptic vesicle
w. Autoinhibition
x. Reuptake
y. Choline esters
z. Cycloplegia
aa. Glaucoma
bb. Pheochromocytoma
cc. Deadly nightshade
dd. Thorn apple
ee. Nicotinic action
ff. SLUD
gg. Yin-Yang effect

21. **What is the pharmacological significance of the following enzymes?**
a. AChE
b. BuChE
c. COMT
d. MAO
e. Adenyl cyclase
f. Acetyltransferase
g. Acetate thiokinase
h. Transacetylase
i. Tyrosine hydroxylase
j. Dopa decarboxylase
k. Phosphorylated AChE
l. Carbamylated AChE

22. **What are the clinical uses of the following drugs:**
a. Atropine
b. Glycopyrrolate
c. Physostigmine
d. Neostigmine
e. Pralidoxime
f. Adrenaline
g. Propranolol
h. Homatropine
i. Sympathomimetics
j. Parasympathomimetics
k. Muscarinic blockers
l. Neostigmine

23. **Which drug you recommend in the following conditions? Give its dose and route of administration:**
    a. Allergic shock in a dog
    b. Ruminal atony in a cow
    c. Glaucoma in a dog
    d. Preanaesthetic antivagal drug in a cow
    e. Ventricular fibrillation in a dog
    f. Relief of heaves in a horse
    g. Antidote for OP insecticide toxicity in a bullock
    h. Preanaesthetic to prevent salivary secretions in a dog
    i. Mydriatic for opthalomological examination
    j. For treating snake/cobra bite in a dog along with antivenin
24. **What is the source (botanical) of the following drugs?**
    a. Atropine
    b. Hyoscine
    c. Pilocarpine
    d. Lobeline
    e. Nicotine
    f. Muscarine
    g. Arecoline
    h. Physostigmine
    i. Reserpine
25. **Substantiate each of the following statements by giving the most appropriate reason/explanation in one or two sentences:**
    a. Nerve impulse conduction and transmission are electrochemical processes.
    b. During depolarization the resting nerve membrane potential reverses to positivity.
    c. During hyperpolarization there is more negativity inside the axon.
    d. During repolarization inside of the axon is momentarily hyperpolarized.
    e. Local anaesthetics block impulse conduction.
    f. Pufferfish toxin/shellfish toxin blocks axonal conducion.
    g. Batrachotoxin blocks nerve impulse conduction.
    h. Parasympathetic nervous system is also called as cholinergic system.
    i. Adrenaline. NorA and dopamine are called catecholamines.
    j. Depolarization preceedes EPSP.
    k. Hyper polarization precedes IPSP.
    l. Hemicholinium inhibits ACh synthesis.
    m. Vesamicol interferes with storage of Ach.
    n. Alpha-bungarotoxin causes skeletal muscle paralysis.
    o. Beta-bungarotoxin causes skeletal muscle paralysis.
    p. Botulinum toxin causes death due to respiration failure.
    q. AChE is called true ChE.
    r. BChE is called pseudo ChE.
    s. Carbidopa inhibits NorA synthesis.
    t. Guanethidine has antiadrenergic effect.
    u. Alpha-methyltyrosine blocks NorA synthesis
    v. Alpha-methyl dopa inteferes with NorA synthesis.
    w. Nicotinic receptors at autonomic ganglia and NMJ are not identical.
    x. Cocaine/imipramine increase NorA actions at effector receptors.
    y. Reserpine depletes NorA stores.
    z. Tyramine fails to produce sympathetic effects in reserpinized animals.
    aa. Indirectly acting adrenergic drugs fail to raise BP in reserpine-pretreated animals.
    bb. Repeated administration of tyramine shows tachyphylaxis on BP in an anesthetized cat.
    cc. Adrenaline causes hyperglycaemia/hyperlipaemia.
    dd. The pharmacological effects of adrenaline are through cAMP.
    ee. The pharmacological effecs of ACh at cellular level are through transduction mechanisms.
    ff. Sympathetic system is called thoracolumbar outflow.
    gg. Parasympahetic system is called craniosacral outflow.
    hh. Sympathetic system is more widely distribted than parasympathetic system.
    ii. AntiChE drugs act as cholinergics.
    jj. Atropine blocks hypotensive response of ACh.
    kk. ACh at high doses in atropinized animals produces tachycardia and rise in BP.
    ll. Homatropine is preferred to atropine in ophthalmology.
    mm. Atropinized animals have disturbed vision.
    nn. Mydriasis produced by adrenaline and atropine is different/not similar.
    oo. Neostigmine is synergistic with antisnakevenom in cobra bite.
    pp. Atropine is used as preanaesthetic.
    qq. Atropine causes xerostomia.
    rr. Pressor reversal of epinephrine is not seen with phenylephrine.
    ss. Dale's reversal occurs following alpha-adrenoceptor blockade.
    tt. Tyramine/Ephedrine is called an indirectly acting sympathomimetic.

uu. Amphetamine is different from other sympathomimetics.
vv. In allergic/anaphylactic shock adrenaline administration is life-saving.
ww. Adrenaline serves as local haemostatic.
xx. Adrenaline potentiates local anaesthesia.
yy. Propranol is used to treat ventricular fibrillation in dogs.
zz. Ganglionic blockade by nicotine and pentamethonium/hexamethonium is different.
aaa. Ganglionic blockade causes hypotension.
bbb. Ganglionic stimulation by nicotine and DMPP is not similar.
ccc. Death in nicotine toxicity is due to respiration failure.
ddd. ACh is also released from postgaglionic sympathetic nerve terminals.
eee. The Ach action at synapse is called `flash like suddenness`
fff. BChE is called nonspecific ChE.
ggg. Ache is called true Che.
hhh. Presynaptic $\alpha_2$ receptors are called autoinhibitory.
iii. NorA release from presynaptic sympathetic nerve terminals is regulated by neuromodulators.
jjj. MAO inhibitors exert antidepressant effect.
kkk. VMA has diagnostic value in pheochromocytoma in man.
lll. MAO inhibition increases NorA stores in sympathetic nerve terminals.
mmm. Termination of action of NorA at effector sites is not mainly through enzymatic inactivation.
nnn. ACh has no clinical application.
ooo. Neostigmine reverses neuromuscular blockade by curariform drugs.
ppp. Ecothiophate/Pysostigmin/Pilocarpine is used in treating glaucoma.
qqq. Carbachol is the most potent choline ester.
rrr. Neostigmine with antisnake venom is beneficial in cobra bite.
sss. Tyramine causes hypertensive crisis in patients receiving MAO-inhibitor antidepressans.
ttt. Phenthiazine derivatives have may be beneficial cardiac arrhhthmia.
uuu. Carbachol is resistant to ChE hydrolysis.
vvv. Atropine causes glaucoma.

26. **Matching the pairs**

a. Somatic nerves: Skeletal muscles
b. Autonomic nerves: Visceral organs
c. Acetylcholine: Choline ester
d. Noradrenaline: Catecholamine
e. Depolarization: Sodium conductance
f. Hyperpolarization: Potassium conductance
g. Tetrodotoxin: Blocks depolarization
h. Saxitoxin: Blocks depolarization
i. Local anaesthetics: Block depolarization
j. Batrachotoxin: Persistent depolarization
k. EPSP: Depolarization
l. IPSP: Hyper polarization
m. AChE: True ChE
n. AChE: Specific ChE
o. BChE: Pseudo ChE
p. BChE: Nonspecific ChE
q. AChE: Nerve junctions/RBC
r. BChE: Plasma/liver
s. AntiChE: Physostigmine
t. Neostigmine: AChE inhibition
u. Arecoline: Cholinergic agonist
v. Vesamicol: Inhibits ACh uptake into vesicles
w. Heicholinium: Inhibits choline uptake
x. Botulinum toxin: Blocks Ach release
y. β-Bungarotoxin: Blocks Ach release
z. $M_1$, $M_3$ and $M_5$ receptors: Gs protein
a. $M_2$ and $M_4$: Gi protein
b. α-methyltyroine: Inhibits tyrosine hydroxylase
c. α-methyldopa: Inhibits Dopa decarboxylase
d. Epinephrine: Adrenal medulla
e. Norepinephrine: Sympathetic nerves
f. Tyramine: Releases NorA
g. Amphetamine: Releases NorA
h. Amphetamine: CNS stimulant
i. Amphetamine: Anorectic
j. $Beta_1$ adrenoceptors: Activate adenyl cyclase
k. $Alpha_2$ adrenoceptors: Inhibit adenyl cyclase
l. $Alpha_1$ adrenoceptor agonist: Phenylephrine/Methoxamine
m. $Alpha_2$ adrenoceptor agonist: Clonidine/Clenbuterol
n. $Beta_1$ adrenoceptor agonst: Dobutaime/Xamoterol
o. $Beta_2$ adrenoceptor agonist: Salbutamol/Salmetrol/Terbutaline
p. $Beta_2$ adrenoceptors: Glycogenolysis
q. $Beta_3$ adrenoceptors: Lipolysis/Thermogenesis
r. $Beta_2$ adrenoceptor antagonist: Butoxamine
s. $Beta_1$ adrenoceptor antagonist: Atenolol/Metoprolol
t. $Alpha_2$ adrenoceptor antagonist: Yohimbine/Idazoxan
u. $Alpha_1$ adrenoceptor antagonist: Prazosin/Doxazocin

v. $M_1$ receptor agonist: McNA 343/Oxotremorine/Mamba Toxin MT7
w. $M_1$ receptor antagonist: Pirenzepine/Oxybutyrin/Atropine
x. $M_2$ receptor antagonist: Gallamine/Atropine
y. $M_3$ receptor antagonist: Ipratropium/Atropine
z. $M_4$ receptor antagonist: Mamba Toxin MT3/atropine
a. $M_5$ receptor anagonist: Atropine
b. Sympathetic system: Thoracolumbar outflow
c. Parasympathetic system: Craniosacral out flow
d. Sympathetic ganglia: Away from organs
e. Parasymathetic ganlia: Close to organs
f. Sympathetic system: Fight or Flight/Spends energy
g. Parasympathetic system: Conserves energy
h. Carbachol: Choline ester
i. Pilocarpine: Cholinomimetic alkaloid
j. Edrophonium: Short acting AntiChE
k. Neostigmine: Reversible antiChE
l. DFP: Irreversible antiChE
m. Ambenonium: AChE inhibitor
n. Pralidoxime: AChE reactivator
o. Atropine: Mydriasis
p. Physostigmine: Glaucoma
q. Atrpine: Deadly nightshade
r. Hyoscine: *Datura straminium/alba*
s. Atropine: Preanaesthetic
t. Homatropine: Ophthalmology
u. Relaxation of sphincter of iris: Atropine
v. Contraction of radial muscle: Adrenaline
w. Atropine: Relief of heaves in horses
x. Physostigmine: Relief of glaucoma
y. Ganglionic stimulant; DMPP/TMA
a. Ganglionic blocker: Mecamylamine/TEA
b. Catecholamine: Dopamine
c. Noncatecholamine: Phenylephrine
d. Isoproterinol; Beta adrenoceptor agonist
e. Physostigmine: Calabar bean/ordeal bean
f. Dopamine: Precursor of Noradrenaline
g. Noradrenaline: Precursor of adrenaline
h. Adrenaline: Adrenal medulla
i. Noradrenaline: Adrenergic nerves
j. Cardiac arrest: Adrenaline
k. Ventricular fibrillation: Propranolol
l. Dichloroisoproterinol: beta adrenoceptor antagonist
m. Alpha-adrenoceptor blockade: Dale's reversal
n. Beta-adrenoceptor blockade: Reduced heart rate and force of contraction
o. Propranolol: Cardiac arrhythmia
p. Phenoxybenzamine: Pheochromocytoma
q. Inhibition of Dopa decraboxylase: Carbidopa
r. Inhibition of tyrosine hydroxylase: Alpha-methyl-p- tyrosine
s. Depletion of NorA granular stores: Reserpine
t. Inhibition of NorA release: Guanethidine
u. Inhibition of NorA re uptake: Cocaine/imipramine
v. $MOA_A$: Specific to Epinephrine and norepinephrine
w. $MOA_B$: Specific to dopamine and 5-HT
x. Alpha-2 adrenoceptor activation: Inhibits adenyl cyclase/Decrease cAMP formation
y. Beta-1 and Beta-2 adrenoceptor activation: Stimulates adenylcyclase/Increase cAMP formation
z. Teritiary amine cholinergic antagonist: Atropine/Benztropine/Oxybutyrin/Dicyclomine/Scopolamine/ Trihexyphenidyl
aa. Quarternary amine cholinergic antagonist: Glycopyrrolate/Ipratropium/Propantheline
bb. Anticholinergic in Parkinson's disease: Benztropine/Trihexyphenidyl
cc. Anticholinergic GI and genitourinary antispasmodic: Dicyclomine/Propantheline
dd. Ophthalmic anticholinergic: Tropicamide/Homatropine/Cyclopentolate
ee. Glycopyrrolate: Anticholinergic antisialic/GI antispasmodic
ff. Oxybutyrin: Smooth muscle antispasmodic/Local anaesthetic activity
gg. Alpha-2 agonist: Clonidine/Gunanafacine/ gunanabenz
hh. Beta adrenoceptor antagonist with quinidine-like activity: Propranolol/Timolol/Bataxolol/Labetolol/ Pindolol
ii. Alpha-1 and Beta-1 adrenoceptor antagonis and partial agonist of Beta-2 adrenoceptors: Labetalol.
jj. Dobutamine: Selective Beta-1 adrenoceptor agonist.
kk. Metyrosine interferes with norepinephrine synthesis.

Q.2. Describe Source, Synthesis, Storage, & pharmacological action of histamine. chemical like 48/90, 19/35L - potent histamine liberator

## CHAPTER - 12: AUTACOIDS (self remedial agents).

Autacoids is derived from two Greek words 'Autos' meaning self and 'Akos' meaning remedial agents, thus collectively called as self remedial agents. These are formed by a variety of cells having diverse physiological as well as pathological roles in the function of body. Some times they are also called as 'local hormones' due to their *de novo* synthesis locally (with a few exceptions) to act locally. The autacoids differ from hormones in that the latter are synthesized and stored in specific endocrine glands to be released into blood, as per the physiological requirement, to be carried to the target tissue or organ, where their effects are manifested). The major functions of autacoids are mediation of reactions of inflammation, allergy and anaphylaxis; modulation of gastric acid secretion, nociception, blood clotting, maintenance of hemodynamics, electrolyte balance and GI motility and as neurotransmitters or neuromodulators.

**Classification of Autacoids**: Based on chemical nature:

A. **Amine Autacoids:** Histamne and 5-hydroxytryptamine.
B. **Peptide Autacoids:** Bradykinin, Angiotensins and Substance P.
C. **Lipid Autacoids: Eicosanoids** (Prostaglandins and Leucotrienes) and platelet activating factor.

(Histo – Tissue. Amine – Basic).

### 1. Histamine

Being an amine (basic) and presence in tissues, so named as histamine after the Greek word 'Histos', meaning tissue. It is present in man and animals, venoms and other zootoxins, bacteria, certain plants and vegetables. Dietary ingestion will not contribute to body histamine since whatever is absorbed is metabolized in liver. Intestinal bacteria can also synthesize histamine, but it is also degraded in liver after absorption.

**Formation, Distribution and Storage**: A basic amine formed from aromatic amino acid L-histidine by histidine decarboxylase. Histamine is formed in almost all tissues, but high concentrations are in GIT, skin and lungs. It is mainly found in mast cells and basophils in association with heparin (in intracellular granules). But it is also present in other cells like histaminocytes in stomach, platelets in blood and histaminergic nerves in brain.

**Histamine Release**: Released from mast cells through exocytosis during anaphylactic/allergic (antigen-antibody reaction) and inflammatory reactions. Certain drugs (histamine liberators) like morphine, dTC, pethidine, stilbamidine, codeine, amphetamine, hydralazine, tolazoline, chlotetracycline etc; proteolytic enzymes like trypsin certain venoms; some food products like crabs, lobsters and fish; surface tension lowering agents like bile salts and surfectants (anionic and cationic) release histamine from mast cells. The chemicals like 48/90 and 19/35L are potent histamine liberators used in experimental pharmacology. In addition, physical, chemical, thermal, cold or radiation injury causes tissue damage accompanied by histamine release. Sodium cromoglycate (used for prevention of asthma in man) prevents histamine release in allergy.

Histamine release in allergic/anaphylactic reactions is blocked by beta-adrenoceptor agonists which activate G-protein-coupled receptors and thereof adenyl cyclase in enhancing cAMP formation (increased cAMP reduces histamine release).

These two Enzy metabolism.

**Histamine Metabolism**: Enzymatically degraded to by histaminase and imidazole N-methyl transferase.

**Physiological Role of Histamine:** The endogenous histamine has both physiological as well as pathological roles:

A. Neurotransmitter in CNS and peripherally; initiates sensory itch and pain at sensory nerve endings. In CNS, regulation of body temperature, CV function and regulation of anterior pituitary hormone release.
B. Role in tissue growth and repair.
C. Stimulation of gastric acid secretion.
D. Regulation of microcirculation in tissues.
E. Regulation of intestinal motility.
F. Role in tissue growth and repair
G. Thermoregulation and control of food and water intake.

In regulation of gastric acid secretion histamine, ACh and gastrin are involved. The mechanism of gastric acid secretion is explained through two hypotheses.

**Single-Cell Hypothesis**: A single parietal cell has $H_2$, $M_2$ and G receptors, which are activated by histamine, ACh and gastrin respectively. The three chemicals act directly on the parietal cell. Activation of $H_2$ receptors increases cAMP and activation of $M_2$ and G receptors increases cytosolic Ca++ . The two second messengers mediate acid secretion into stomach.

**Two-Cell Hypothesis**: Gastrin and ACh act either only by releasing histamine or partly by releasing histamine and partly by directly activating their receptors on the parietal cell.

**Pathological Role of Histamine:**

A. Mediator of reactions allergy and anaphylaxis (hypotensive crisis, increased vascular permeability and intense constriction of bronchi/bronchioles: Histamine shock).
B. Genesis of peptic ulcer (hyper gastric acidity)
C. Mediation of vasodilatation and other responses of inflammation.
D. Role in genesis of headache.
E. Induction of vomition (central).
F. Intense skin itching in infections and parasitic infestation.

**Histamine Receptors:** The effects of histamine are due to activation of histamine receptors, which are classified as $H_1$, $H_2$, $H_3$ and $H_4$ receptors. The location, effects, agonists and antagonists of histamine receptors are as below:

| Receptor | Location/Tissue | Effects of Activation | Agonists | Antagonists |
|---|---|---|---|---|
| $H_1$ | Smooth muscles in intestines, bronchi, blood vessels, uterus and brain (post-synaptic), CTZ, afferent nerve endings | Contraction of intestines, bronchi/bronchioles and uterus. CNS excitation. Dilatation of blood vessels, increased capillary permeability and oedema. Mediator of allergic/ anaphylactic and inflammatory reactions. Vomition. Stimulation afferent nerve endings. | Histamine 2-Methyl histamine | Mepyramine, promethazine, diphenhydramine, triplennamine, pheniramine, astemizole, cetrizine etc. Not effective in suppressing acute inflammatiory responses. |
| $H_2$ | Gastric parietal cells mucosa, heart and brain (pre synaptic). Cat trachea. Sheep bronchi. Rat uterus | Gastric acid secretion. Vasodilatation (relaxation of vascular smmoth muscle. Increase in rate and cardiac out put. CNS excitation. | Histamine Dimaprit | Cimetidine, ranitidine, nizatidine, famotidine |
| $H_3$ | Brain (presynaptic) | Transmitter. Inhibition of other transmitters. Excitation and autoinhibition in CNS | Histamine α-methyl histamine | Thioperamide |
| $H_4$ | Intestines, spleen, thymus, T cells, neutrophils and eosinophils | Contributor to inflammatory responses? | Histamine | |

All the four histamine receptors are G-protein-coupled receptors. $H_1$ activates phospholipase C-Inositol phosphate system formation of second messengers $IP_3$ and DAG. $H_2$ receptors activate adenylcclase-cAMP system. $H_3$ receptors inhibit adenylcyclase-cAMP system (interfering with $Ca^{++}$ influx and activation of $K^+$ channels.

**Pharmacological Effects of Histamine:**

a) **On Vascular Smooth Muscles:** Intense vasodilatation ($H_1$ and $H_2$ mediation) in capillary bed in all small blood vessels in general causing a hypotensive crisis. However, histamine has constrictor effect on large blood vessels and its intensity is species-dependent. In rabbit the constrictor effect is more prominent than the dilator effect resulting in increase in BP.

**Histamine Shock**: The intense dilatation of capillary bed is accompanied by increased capillary permeability ($H_1$ through EDRF and $PGI_2$). The capillary endothelial cells constrict exposing the endothelial membrane (gaps in between junctions), which becomes freely permeable to plasma (along with proteins) lowering the blood volume. The dilated arterioles, venules and capillaries tap large volumes of blood reducing the venous return and cardiac output. The condition is precipitated by respiratory distress due to intense constriction of respiratory passages.

b) **On Heart:** Histamine has a direct stimulatory effect, both positive inotropic and chronotropic effects. Increases coronary blood flow. At high doses causes ventricular arrhythmia ($H_2$).

c) **Triple Response:** Intra-dermal injection of histamine (10-20 micrograms) in man causes a characteristic triple response ($H_1$):
   a. Intense reddening at the point of injection, called 'flush' (vasodilatation of arterioles at the spot).
   b. The surrounding flare (redness) due to axon reflex through sensory nerve fibres and release of vasodilator mediator CGRP (calcitonin gene-related peptide).
   c. Wheal formation due to increased dilatation and permeability and escape of fluid from capillaries and venules.

d) **On Extravascular Smooth Muscles:** Acute bronchial constriction (guinea pig most sensitive to histamine-induced bronchospasm,). Tracheal relaxation in cat ($H_1$ and $H_2$). Bronchial relaxation in sheep ($H_2$). Relaxation of rat uterus ($H_2$), but contraction in other species ($H_1$). Contraction of intestinal smooth muscles causing increase in tone and motility of intestines (ileum of guinea pig most sensitive, hence used for bioassay of histamine; rats and mice are highly resistant).

e) **On Exocrine Glands:** Promotion of gastric acid secretion through $H_2$ receptors stimulation.

f) **On CNS:** Injected histamine cannot cross the BBB. Endogenous histamine (in brain) serves neurotransmitter function. CNS excitation ($H_1$). Exerts autoinhibitory control of synthesis and release of histamine acting presynaptically ($H_3$)

g) Histamine causes itch and pain on intracutaneous injection due to stimulation of sensory nerve endings.

Histamine has no therapeutic application, but only used in experimental pharmacology. Its isomer **betazole** is used in testing gastric acid secretogogue function in man.

## 2. Antihistamines

These drugs antagonize (competitive antagonists of histamine at receptors) the effects of histamine released in the body. Sympathomimetics (epinephrine, norepinephrine and ephedrine) are physological antagonists of histamine.

**Classification:**

**A. Based on Chemistry:**

a) **Ethanolamine Derivatives:** Diphenhydramine and dimenhydrinate
b) **Ethylenediamine Derivaties:** Tripelennamine, mepyramine and pyrillamine
c) **Alkylamine Derivaties:** Chlopheniramine and triprolidine
d) **Piperazine Derivatives:** Cetrizine, cinnarizine, meclizine and chlorcyclizine
e) **Phenothiazine Derivatives:** Promethazine and trimeprazine
f) **Piperidine Derivatives:** Fexofenadine and loratidine

**B. Based on Pharmacological Actions (Peripheral $H_1$ Blockade and CNS action):**

a) **Potent Antihistaminic Action and Sedation:** Promethazine, diphenhydramine and dimenhydrinate
b) **Potent Antihistaminic Action, but less Sedation:** Tripelennamine, chlorcyclizine and chlorpheneramine
c) **Less Potent Antihistaminic and Sedation:** Mepyramine and phenindamine
d) **Antihistaminic Action, but no Sedation:** Loratadine and terfenadine

**C. Based on Receptor Specificity:**

a) **$H_1$ Blockers:** Diphenhydramine, promethazine, chlorpheneramine, triplennamine, mepyramine, pheniramine, meclizine, cetrizine
b) **$H_2$ Blockers:** Cimetidine, rantidine, nizatidine and famotidine
c) **$H_3$ Blockers:** Thioperamide

Histamine analogues methyl histamine and betazole are agnosits on $H_1$ and $H_2$ receptors respectively.
The antihistamines with antimuscarinic activity are clemastine, diphenhydramine, methdilazine and promethazine.

**Pharmacological Effects of Antihistamines:**

**Effects Due to Antagonism of Antihistaminic Action:**

The $H_1$ antihistamines block the effects of histamine on intestines, bronchi, uterus and blood vessels; hypotensive effect in cats and dogs; and reduce the triple response, skin itching and urticaria. The $H_1$ antagonism effectively results in immediate type histamine-induced allergic/anaphylactic manifestations (urticaria, itching, oedema and fall in BP). The $H_1$ blockers do not prevent histamine-induced gastric acid secretion.

**Effects Independent of Histamine Antagonism:**

a) **Seadtion:** Majority of the $H_1$ blockers administered for antihistaminic purpose produce varying degrees of sedation and/or drowsiness. Sedation is potentiated when used with barbiturates, benzodiazepine tranquilizers or other CNS depressants.
b) **Antiemetic Effect:** Phenothiazine derivative antihistamines have antiemetic effect and are useful in motion sickness-induced vomition (Promethazine, trimeprazine cetrizine, cinnarizine, meclizine and chlorcyclizine)
c) **Autonomic Effects:** Dryness of mouth (anti-muscarnic effect) by many $H_1$ blockers and adrenergic blockade by antazoline and phenindamine. Antipruritic effect of antihistamines in part is due to sedative, anticholinergic, antiserotoninergic and local anaesthetic effects.
d) **Local Anaesthetic action**; but not clinically used since SC injection causes marked irritation (stimulation of sensory nerve endings)..

**Therapeutic Application of $H_1$ Antihistamines**

a) In allergic and anaphylactic reactions (along with epinephrine)
b) Relief of bronchial asthma, laminitis, azoturia and pulmonary emphysema in horses.
c) In bloat, acetonaemia, gangrenous mastitis, metritis and retained placenta.
d) Dermatitis, pruritis and eczema.

| Antihistamine | Administration: Dose and Route of Administration | |
|---|---|---|
| | Small Animals | Large Animals |
| Diphenhydramine | 2 – 3 mg/kg, orally or IV | 0.5 – 1 mg/kg orally or IV |
| Promethazine | 0.5 – 1 mg/kg orally, IM or IV | 1 – 2 mg/kg IM |
| Pyrillamine | 1 – 2 mg/kg IM, SC or IV | 0.5 – 2 mg/kg SC, IM or IV |
| Dimemhydrinate | 1 – 1.5 orally, IM or SC | 0.5 – 1.5 mg/kg orally, SC or IM |
| Chlorpheniramine | Dog: 0.5 mg/kg orally at 8 hr intervals<br>Cat: 2-4 mg at 12 hr intervals | |
| Triplennamine | | 0.5 mg/kg IM thrice a day |

The $H_2$ blockers are used in treating peptic (gastric) ulcer in man. These also block cardiac effects of histamine. Also helpful in treating NSAID-induced gastric ulcer in dogs.

**Toxicity of Antihistamines:** In high doses cause ventricular arrhythmia and CNS excitation, even convulsions.

### 3. 5-Hhydroxytryptamine (Serotonin/Vasotonin/Enteramine)

**Biosynthesis, Distribution and Breakdown:**

Formed from dietary L-aromatic amino acid tryptophan:

Tryptophan → 5-Hydroxytryptophan → 5-Hydroxytryptamine (5-HT)

Tryptophan hydroxylase; Dopa decarboxylase

5-HT synthesis occurs in entero chromaffin cells and neurons, but not in platelets. However, 5-HT enters platelets by a strong uptake process. 5-HT is metabolized through MAO to 5-hydroxyindoleacetic acid and by dehydrogenase to 5-hydroxytryptophol, which are excreted through urine. 5-HT is also ingested through diet. However, most of it is degraded in the intestines. Almost all body's 5-HT (90%) is present in enterochromaffin cells in GIT (stomach and small intestine). Also present in nerve cells of myenteric plexuses as an excitatory transmitter, platelets in blood and as a transmitter in mid brain. It is also widely distributed in plants, venoms and toxins.

**Patho-physiological Role**

A. Neurotransmitter in CNS: Regulation of body temperature, behaviour, mood and sleep, hallucinations, appetite, vomiting, and pain perception.
B. Precursor of melatoin in pineal gland: Regulation of biological clock.
C. Neuronal regulation of secretion of anterior pituitary hormones.
D. Role in blood coagulation (platelet aggregation)
E. Regulation of intestinal motility. Initiates peristaltic reflex due to mechanical stimulus of pressure.
F. Microvascular control.
G. Vomiting
H. Mediator of inflammatory responses
I. Migraine, mood disorders and anxiety.

**5-HT Receptors:**

| Receptor | Agonists | Antagonists |
|---|---|---|
| $5\text{-HT}_{1A}$ | Buspirone (partial) | Spiperone<br>Ergotamine (partial)<br>Methiothepin |
| $5\text{-HT}_{1B}$ | Ergotamine (partial) | Methiothepin |
| $5\text{-HT}_{1D}$ | Sumatriptan | Methiothepin<br>Ergotamine (partial) |
| $5\text{-HT}_{2A}$ | LSD<br>α-Methyl 5-HT | Ketanserin<br>Cyproheptadine<br>Methysergide |
| $5\text{-HT}_{2C}$ | LSD<br>α-Methyl 5-HT | Methysergide |
| $5\text{-HT}_3$ | 2-Methyl 5-HT<br>Chlorophenylbiguanide | Ondansetron<br>Tropisetron<br>Granisetron |
| $5\text{-HT}_4$ | Metoclopramide | Nil |
| $5\text{-HT}_5$ | Nil | Nil |
| $5\text{-HT}_6$ | Nil | All $5\text{-HT}_2$ antagonists |
| $5\text{-HT}_7$ | LSD | Nil |

All the 5-HT receptors are G-protein-coupled receptors, except 5-$HT_3$ which are ligand gated cation ($Na^+$ and $K^+$) channel receptors (activation results in fast depolarization). The 5-$HT_1$ receptor activation inhibits adenylcyclase-cAMP pathway or activation of phospholipase C-Inositol pathway (IP). The effects of 5-$HT_{4, 6}$ and $_7$ are due to activation of adenylcyclase and/or phospholipase C-IP pathways.

**Pharmacological Effects of 5-HT and Receptors Involved:**

a) **GI Tract:** Direct stimulatory effect on intestinal smooth muscles (5-$HT_2$ receptors) and indirectly through activation of 5-$HT_3$ and 5-$HT_4$ receptors on enteric neurons. Stimulates intestinal secretions and causes nausea and vomiting through activation of 5-$HT_3$ and 5-$HT_4$ receptors in smooth muscles and sensory nerve endings.
b) **Vascular Smooth Muscle:** Large veins and arteries in periphery are constricted (5-$HT_{2A}$ receptors). Constriction of large intracranial veins (5-$HT_1$ receptors). Also causes vasodilatation indirectly through release of NO from endothelial cells and inhibition of NorA release from sympathetic nerve terminals.
c) **Nonvascular Smooth Muscle:** Contraction of uterus and bronchial tree (5-$HT_{2A}$ receptors).
d) **Blood:** Causes aggregation of platelets (5-$HT_{2A}$ receptors).
e) **Nerve Endings:** Stimulates nociceptive sensory nerve endings. Nettle stings cause intense pain due to presence of 5-HT (5-$HT_3$ receptors).
f) **CNS:** Exerts excitatory or inhibitory effects acting presynaptically and/or postsyaptically. Hallucinogenic effects and 'wet-dog shakes' (5-$HT_{2A}$ receptors). Necessary for normal sleep.

**5-HT Antagonists:** Competitive Antagonists: These drugs have varied therapeutic uses:

a) Treatment of migraine in man (dihydroergotamine, methysergide)
b) T promote appetite (cyproheptadine, ketanserin)
c) Antiemetics or anxiolytic (ondansetron and tropisetron)
d) To stimulate gastric emptying (metoclopramide)

**4. Kinins: Kallidin and Bradykinin**

**Formation: Kallikrin-Kininogen-Kinin System:** During inflammation the Hageman factor (HF), prekallikrein and kininogen leak out from the capillaries with plasma into the damaged tissue spaces. HF, present normally in an inactive form in blood plasma, is activated during tissue damage due to contact with glass, collagen, basement membrane, bacterial polysaccharides urate crystals etc. The activated HF converts prekallikreins to kallikreins (proteinases), which in turn convert a high molecular weight kininogen to bradykinin (BK) and a low molecular weight kininogen to kallidin. Both BK and kallidin have similar actions. BK is enzymatically inactivated by kininases.

**Patho-physiological Role:** BK produces its effects by activating its receptors ($B_1$ and $B_2$), G-protein-coupled receptors, located on the cell membrane of effector cells. $B_1$ receptors are absent in normal tissues, but are induced by interlukin-I due to tissue injury and inflammation. $B_2$ receptors are present in normal tissues. The vascular effects of BK are mediated by increased formation of $PGI_2$ and NO. The effects of BK include:

A. Mediator of reactions of inflammation (pain, vasodilatation, increased vascular permeability and smooth muscle spasm).
B. Controls blood flow in exocrine glands and their secretion.
C. Stimulates ion transport in epithelia and secretion in intestines (excess BK causes diarrhoea), respiratory tract (allergic rhinitis) and gall bladder.
D. Increase in pain sensation (stimulation of pain nerve endings).
E. Contraction of smooth muscles in intestines and uterus.

**4. Angiotensins**

**Formation: Renin-Angiotensin System;** Renin (secreted from JG cells) converts angiotensinogen to angiotensin I (decapeptide) which is converted to angiotensin II (octapeptide) by an enzyme angiotensin converting enzyme (ACE). This system has role in homeostasis of haemodynamics: Regulation of arterial blood pressure and sodium and water (extra cellular fluid volume) balance. Renin is secreted from JG cells

due to reduced renal blood flow, decreased glomerular filtration and low $Na^+$ concentration in distal tubular fluid. Renin being a proteolytic enzyme converts angiotesinogen (a plasma globulin) to angiotensin I, which in turn is converted to angiotensin II by antgiotensin converting enzyme (ACE). Angiotensins III and IV are formed from angiotensin II by the action of aminopeptidase A and aminopeptidase N respectively. Angiotensin I has no appreciable activity. Angiotensin II promotes vasscular growth (hyperplasia and hypertrophy), causes intense vasoconstriction (direct and through release of Norepinephrine from sympathetic nerve endings) and salt retention (enhanced tubular reabsorption due to aldosterone secretion). Angiotensin III stimulates aldosterone secretion and thirst. Angiotensin IV releases plasminogen activator inhibitor-I from the endothelium which promotes thrombosis.

Renin secretion is stimulated by enhanced renal sympathetic activity, β-adrenoceptor agonists and $PGI_2$, and inhibited by atrial natriuretic peptide (ANP). Enalakiren is a renin inhibitor reduces plasma renin activity.

**Patho-physiological Role:** Angiotensins produce their effects through activation of angiotensin receptors ($AT_1$ and $AT_2$), which are G-protein-coupled receptors (inhibition of adenyl cyclase-cAMP pathway and activation of Phospholipase C-$IP_3$ and DAG system)). The effects of angiotensins include:

A. Increase in aldosterone secretion from adrenal cortex and promotion of renal tubular reabsorption of sodium.
B. Maintenance of fluid-electrolyte balance and control of thirst.
C. Potent direct constrictor action on smooth muscles of blood vessels and indirectly through release of NorA from sympathetic nerve terminals and epinephrine from adrenal medulla.

**ACE Inhibitors:** These are drugs which inhibit ACE and prevent formation of angiotensin II and prevent vasoconstriction (vasodilatation) and lower sodium retention. ACE inhibitors are captopril, enalapril, lisinopril, ramipril, fosinopril, perindopril and benazepril. Enalapril, perindopril, ramipril and benezapril are prodrugs, which upon metabolic activation form enalaprilat, perindoprilat, ramiprilat and benazeprilat respectively. The ACE inhibitors are used as antihypertensives in man and are of value in treating CHF in dogs (In the genesis of CHF rennin-angiotensin pathway is activated causing Na retenion, oedema and increased vascular resistance).

Enalapril in dog to treat CHF: 0.5 mg/kg once or twice depending upon severity for 1 or 2 weeks by critical ECG monitoring and clinical situation. Benezapril in dog and cat: 0.25-0.5 mg/kg/day orally Lisinopril in dog: 0.5 mg/kg/day orally.

**Angiotensin Antagonists:** These drugs antagonize the actions of angiotensin II by blocking the AT1 receptors (competitive antagoinists). The drugs are: Losartan, valasartan, irbesartan and candesartan

## 5. Eicosanoids

The biologically active compounds derived from 20 carbon atom unsaturated fatty acid arachidonic acid (5,8,11,14-eicosatetraenoic acid: Eicosa = 20 carbon; tetraenoic = four double bonds). Eicosanoids are not preformed and/or stored like histamine, but are generated *de novo*, from cell membrane phospholipids. The eicosanoids are prostaglandins and leukotrienes. Originally, a substance present in human seminal plasma which caused contraction of uterus and intestine and produced vasodilatation was named as prostaglandin, the substance was thought to be secreted from prostate gland (von Euler, 1935). Later the seminal substance was found to be a mixture of several closely related substances. Now it is known that there are a number of different types of such substances found in many tissues, but the name still continues.

**Formation: Biosynthesis**: The first step in the formation of eicosanoids is release of a 20-carbon poly unsaturated fatty acid arachidonic acid from, cell membrane phospholipids by the action of phospholipase A2. The stimuli for activation of this enzyme are either physiological or pathological (tissue injury, thrombin formation, antigen-antibody reaction etc). The free arachidonate is metabolized by different pathways leading to the formation of eicosanoids namely prostaglandins and thromboxanes by the action of cyclooxygease (COX), which exists in two forms COX-1 and Cox-2, and leukotrienes by the action of 5-lipoxygenases (5-LPO). The end products of arachidonate-COX pathway are prostanoids: Prostacyclin

($PG1_2$), Thromboxane ($TXA_2$) and Prostaglandins ($PGF_2\alpha$, $PGD_2$ and $PGE_2$) whose formation is catalysed by prostacyclin synthetase, thromboxane synthetase and prostaglandin isomerase respectively.
COX exists in 2 forms: COX-1 as a normal constituent in most cells responsible for formation of prostaglandins necessary for homeostasis or physiological functions. The COX-2 is induced in inflammatory cells by an inflammatory stimulus (pathologic or pharmacological).

**Patho-physiological Role of Prostaglandins:**

A. CVS : Vasodilation/constriction, control of vascular tone and BP
B. Role in platelet aggregation.
C. Control of uterine contractions.
D. Protective role on gastric mucosa against gastric acid.
E. Regulation of tone of bronchi and intestines.
F. Regulation of renal function.
G. Role in inflammation.
H. Role in nociception.
I. Neuromodulator in CNS
J. Role in release of anterior pituitary hormones.
K. Role in metabolism: Lipolysis, release of insulin and calcium metabolism.

**Prostanoid Receptors:** These are G-protein-coupled receptors whose effects are mediated through transduction mechanisms involving cAMP or $IP_3$/DAG. DP and IP receptor activation relaxes vascular smooth muscles and prevents platelet aggregation through increase in cAMP formation. $EP_1$ and FP receptor activation causes smooth muscle contraction through $IP_3$/DAG pathway. $EP_2$ receptors relax smooth muscles by increasing cAMP. TP receptor effects (smooth muscle contraction and platelet aggregation) are mediated through $IP_3$/DAG transduction mechanisms. The receptors are classified into five major groups according to their primary prostanoid agonist as below:

| Receptor | Prostanoid Agonist | Major Effects |
|---|---|---|
| DP | $PGD_2$ (also $PGE_2$) | From mast cells. Vasodilatation and prevention of platelet aggregation |
| FP | $PGF_{2a}$ | Contraction of uterus in human. Luteolysis in animals. Bronchoconstriction in cat and dog |
| IP | $PGI_2$ | Vasodilatation. Prevention of platelet aggregation. Renin release and Na reabsorption. |
| TP | $TXA_2$ | Vasoconstriction. Aggregation of platlets. Bronchoconstriction |
| EP:Subtypes: | | |
| $EP_1$ | $PGE_2$ | Constriction of smooth muscles of bronchi and GIT |
| $EP_2$ | $PGE_2$ | Dilatation of bronchi and blood vessels. Increase in intestinal secretions. Relaxation of GIT |
| $EP_3$ | $PGE_2$ | Contraction of intestines. Inhibition of gastric acid secretion and stimulation of gastric mucus secretion. Inhibition of lipolysis. Contraction of uterus in pregnant women. |

**Effects of Prostanoids:**

1. **$PGD_2$:** Vasodilatation, inhibition of platelet aggregation, relaxation of GI smooth muscles, modification of release of hypothalamic/pituitary hormones and bronchoconstriction.
2. **$PGF_{2a}$:** Myometrial contraction (humans), luteolysis (cattle) and bronchoconstriction (cats and dogs).
3. **$PGI_2$:** Vasodilatation, inhibition of platelet aggregation, protection on gastric mucosa (control acid secretion), renin release and sensitization of sensory nerve endings to pain inducers (bradykinin, hitamine and substance P).

4. **$TXA_2$:** Vasoconstriction, platelet aggregation and bronchoconstriction.
5. **$PGE_2$:** Constriction of bronchial and intestinal smooth muscles ($EP_1$ receptors). Bonchodilatation, vasodilatation, stimulation of intestinal fluid secretion and relaxation of GI smooth muscle ($EP_2$ receptors). Contraction of intestinal smooth muscle, inhibition of gastric acid secretion, increased gastric mucus secretion, inhibition of lipolysis, inhibition of autonomic neurotransmitter release, stimulation of contraction of pregnant human uterus and sensitization of sensory nerve endings to pain inducers (bradykinin, hitamine and substance P).

**Prostanoids in Inflammation:**
Inflammatory response is always accompanied by release of prostanoids, mainly the $PGE_2$ and $PGI_2$ from local tissue cells and blood vessels and $PGD_2$ from mast cells.
$PGE_2$, $PGI_2$ and $PGD_2$ are powerful vasodilators and are synergistic with other inflammatory vasodilators such as histamine and bradykinin: causing redness in acute inflammation due to dilator action on precapillary arterioles. These also potentiate the capillary permeability of histamine and also potentiate pain-inducing effect of bradykinin. The antiinflammatory actions of NSAIDs are largely due to prevention of these effects of prostaglandins. $PGE_2$ also causes fever (antipyretic action of NSAIDS is inhibition of synthesis $PGE_2$ in hypothalamus).

$PGF_{2a}$ also exerts antiinflammatory role through decrease in release of lysosomal enzymes and histamine from mast cells and generation of toxic oxygen metabolites from neutrophils.

**Clinical Application of Prostaglandins:**
Synthetic analogues of PG are of great clinical value in human medicine:

a) For termination of pregnancy ($PGE_2$ agonists: gemeorost and misoprostol; $PGF_{2a}$ analog: carboprost).
b) For induction of labour ($PGE_2$ analog: dinoprostone; $PGF_{2a}$ analog: carboprost).
c) To arrest post-partum haemorrhage ($PGF_{2a}$ or $PGE_2$ analogs).
d) In peptic ulcer ($PGE_1$ analogs: misoprostol and rioprostil; $PGE_2$ anolog: enprostil)

The obstetric use of PG analogs is advised when the conventional oxytocics (oxytocin or ergot alkaloids) do not show satisfactory response.

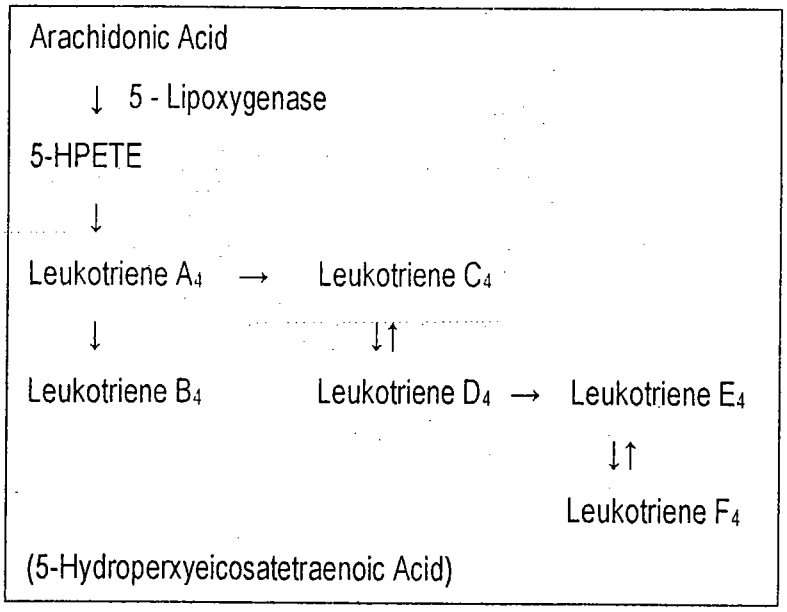
**In veterinary medicine $PGF_{2a}$** or its analogues are used for

a. Luteolytic effect for induction of oestrus/synchronization of oestrus.
b. Termination of pregnancy or expulsion uterine debris in cattle, sheep and dogs (alone or in combination with corticosteroids or in dogs sulpiride a $D_{2/3}$ antagonist). Coticosteroids and sulpiride potentiate uterine contractions.

The $PGE_1$ anologs misoprostol and rioprostil and $PGE_2$ analog enprostil may also be useful NASAID-induced gastric ulceration/haemohrrage in dogs.

**Leucotrienes**
These are formed by the action of 5-lopoxygenase enzyme on arachidonic acid. The enzyme is present in cytosol in lungs and blood (platelets, mast cells and WBC). Their formation proceeds as below:

**Biosynthesis of Leukotrienes**




The SRS-A (slow-releasing-substance of anaphylaxis) constitute $LTC_4$, $LTD_4$ and $LTE_4$

**Effects of Leukotrienes**: The leukotrienes have role in inflammation and produce effects through activation of LT receptors, which are G-protein-coupled receptors (effects are mediated through phospholipase C-$IP_3$/DAG transduction pathways).

1. $LTB_4$ causes adherence, chemotaxis and activation of polymorphs and monocytes and stimulation of cytokine production from macrophages and lymphocytes. Contributes to pain (sensitizes afferent nerves) and inflammatory responses.
2. $LTC_4$, $LTD_4$ and $LTE_4$ cause constriction of bronchial smooth muscle, constriction of coronary vessels and dilatation in many other blood vessels.

Zileutin inhibits 5-lipoxygenase and interfers with leukotriene formation. Zarfirlukast and montelukast the antagonists of cysteinyl leukotrienes ($LTC_4$, $LTD_4$ and $LTE_4$) are used in treating asthma in man.

## 6. Platelet Activating Factor

The platelet activating factor (PAF) formed by acetylation of lyso-glyceryl phosphorylcholine (by acetyl CoA), another breakdown product of arachidonate by the action of phospholipase $A_2$ in inflammed cells. It is formed and released from eosinophils, macrophages, neutrophils, vascular endothelium and by thrombin stimulation from platelets. It also has role in mediating inflammatory reactions. Its effects produced through activation of PAF receptors (G-PC receptors involving formation of $IP_3$/DAG transduction mechanisms)

**Pathophysiological Role:**

a) Mediator of inflammatory responses (vasodilatation, exudation, chemotaxis, pain etc).
b) Bronchial constriction in association with leukotrienes (bronchial asthma).
c) Allergic/anaphylactic responses.
d) Promotion of platelet aggregation and thrombus formation.
e) Facilitation of implantation of embryo.
f) Initiation of parturition at the term.

**Effects of PAF**:

a) Aggregation of platelets and release of TXA2.
b) Vasodilatation, increase in vascular permeability (oedema or wheal formation when injected intradermally).
c) Chemotactic for neutrophils, monocyes and eosionophils
d) Bonchoconstriction (bronchial asthma) and stimulates intestinal and uterine contractions.

e) Induces gastric bleeding and promotes gastric ulceration.
f) Increases eicosanoid formation by activating phospholipase $A_2$.

Corticosteroids exert antiinflammatory action through inhibition of PAF synthesis.

## EXERCISE

1. Describe the source, synthesis and storage of histamine in the body. Discuss its pharmacological actions.
2. Describe the patho-physiological significance of histamine. Discuss the clinical application of antihistamines in veterinary practice.
3. Name the histamine receptors along with their location, agonists and antagonists. Discuss the clinical value of antihistamines in veterinary practice.
4. Describe the pharmacological actions of histamine along with associated receptors.
5. Classify the antihistamines. Discuss their pharmacological effects and clinical value.
6. What are autacoids? Give their classification and state in brief the physiological significance of each one of them.
7. Name the amine autacoids and write about their biosynthesis, storage and pathophysiological significance.
8. What are autacoids? Describe the role of autacoids as mediators of inflammatory responses?
9. Name the peptide autacoids. Discuss the homeoastatic role of renin-angiotensin system.
10. What are eicosanoids? Discuss the physio-pathological role of lipid derived autacoids.
11. Describe the biosynthesis of prostaglandins. Discuss the clinical application of prostaglanins in veterinary practice.
12. Name the angiotensins, state how they are formed. Discuss their physiological significance.
13. What are prostanoids? Enlist their pharmacological effects and discuss their role in inflammation.
14. What are prostaglandins? Enlist the different prostanglandins and state their patho-physiological role.
15. **Write a short note the following**:
    a) Antihistamines
    b) Histamine liberators
    c) Triple response
    d) Histamine shock
    e) Angiotensins
    f) Renin-angiotensin system
    g) Synthesis of eicosanoids
    h) Prostaglandins
    i) Leukotrienes
    j) Cyclooxygenases
    k) PAF
    l) Kinins
    m) 5-HT/Serotonin
    n) Histamine receptors
    o) Role of endogenous histamine
    p) Allergic/Anaphylactic shock
    q) Patho-physiological role of 5-HT
    r) ACE inhibitors
16. **Differentiate between the following**:
    a) Prostaglandins & Leukotrienes
    b) $H_1$ Blockers & $H_2$ blockers
    c) Autacoid & Hormone
    d) Kallidin & Bradykinin
    e) Angiotensin I & Angiotensin II
    f) Histamine & Betazole
    g) COX I and COX II
    h) Cyclooxygenase & Lipooxygenase
    i) Phospholipase $A_2$ & Cyclooxygenase
    j) Promethazine & Ranitidine
    k) Reserpine & Guanethidine
17. **State the pharmacological/physiological significance of the following enzymes**:
    a) Cyclooxigenase I
    b) Cycloxygenase II
    c) Histaminase
    d) Histidine decarboxylase
    e) Tryptophan hydroxylase
    f) Dopa decarboxylase
    g) Kininases
    h) ACE
    i) Phospholipase $A_2$
    j) Prostaglandin isomerase
    k) 5-Lipoxygenase
    l) Aminopeptidase A
    m) Aminopeptidase N
    n) Renin
18. **State in brief the exact mode of action of the following drugs and indicate the associated clinical application**:
    a) Diphenhydramine
    b) Cimetidine/Nizatidine
    c) Methysergide/Ketanserin
    d) Benazepril/Lisinopril
    e) Losartan/Valasartan
    f) PGF2α/Carboprost
    g) NSAIDs/Aspirin
    h) Misoprostol
    i) Zileutin
    j) Zafirlukast/Montelukast
    k) Enalakiren
    l) Sodium cromoglycate

19. **What do you mean by the following? Answer in one sentence for each:**
    a) Autacoid
    b) Eicosanoids
    c) Leukotrienes
    d) Prostaglandins
    e) Cyclooxygenases
    f) Angiotensins
    g) Kinins
    h) Serotonin
    i) PAF
    j) ACE inhibitor
    k) Histamine liberator
    l) Histamine shock
    m) Triple response
    n) Wet dog shakes
    o) Bradykinin
    p) Angiotensinogen
    q) Renin
    r) Prostanoids
    s) Arachidonic acid
    t) Lipooxygenase
    u) SRS-A

20. **Write the clinical value of the following categories of drugs:**
    a) Antihistamines
    b) $H_2$ antagonists
    c) 5-HT antagonists
    d) ACE inhibitors
    e) Angiotensin antagonists
    f) Renin antagonists
    g) COX inhibitors
    h) $PGE_1$ agonists
    i) $PGF_{2\alpha}$ agonists
    j) Leukotriene antagonists

21. **Give the most appropriate reason in one or two sentences for each of the following statements:**
    a) The traditional/common antihistamines are not useful in treatment of gastric acidity.
    b) In histamine shock death is due to vascular shock.
    c) In anaphylactic shock death is due to respiration failure.
    d) Respiratory distress is seen in severe anaphylactic reaction.
    e) In allergic/anaphylactic reactions adrenaline is a life saving drug.
    f) Antihistamines give relief in allergic reactions.
    g) Cimetidine/Ranitidine is of value in treating peptic ulcer.
    h) Captopril/Enalapril is used as an antihypertensive drug.
    i) ACE inhibitors are used as antihypertensives.
    j) Renin secretion promotes sodium retention
    k) Dietary histamine does not contribute to body histamine stores.
    l) Autacoids are not hormones.
    m) Basophils are also called circulating counterparts of mast cells.
    n) Sodium cromoglycate prevents asthmatic attacks in asthma.
    o) Beta-adrenoceptor agonists can be used to counter allergic/anaphylactic reactions.
    p) Histamine is physiologically important for the animal.
    q) Betazole is used as a diagnostic tool.
    r) Phenothiazine/Piperazine antihistamines are useful in motion sickness.
    s) Antihistamines are of value in treating pruritis in dogs.
    t) 5-HT is also called serotonin/vasotonin/enteramine.
    u) 5-HT antagonist metoclopramide is used as a prokinetic.
    v) Angiotensin II promotes sodium retention.
    w) Enalapril/Benezepril is a prodrug.
    x) ACE inhibitors are of value in treating CHF in dogs.
    y) $AT_1$ antagonists can be used as vasodilators/antihypertensives.
    z) COX I is a constitutive enzyme.
    aa) COX II is an inducible enzyme.
    bb) Prolonged use of aspirin results in delayed blood clotting.
    cc) Zarfirlukast/Montelukast relieves asthma.
    dd) Misoprostol is administered along with NSAIDs
    ee) As anti-inflammatory drugs selective COX II inhibitors are preferred to nonselective COX inhibitors.
    ff) $PGF_{2\alpha}$ is used for synchronization of oestrus.

22. **Matching** (correct pairs):
    a) Histamine: Amine autacoid
    b) 5-HT: Amine autacoid
    c) Bradykinin: Peptide autacoid
    d) Angiotensin: Peptide autacoid
    e) Prostaglandin: Lipid autacoid
    f) Leukotriene: Lipid autacoid
    g) Morphine/Pethidine: Histamine liberator
    h) Mepyramine: Antihistamine
    i) Dimaprit: $H_2$ agonist
    j) Nizatidine: $H_2$ antagonist
    a) Thioperamide: $H_3$ antagonist
    b) Cetirizine: $H_1$ antagonis

c) Ketanserin: 5-HT antagonist
d) Metoclopramide: Prokinetic
e) Bradykinin: Vasodilator
f) Enalakiren: Renin inhibitor
g) Ramipril: ACE inhibitor
h) Irbesartan: Angiotensin antagonist
i) Prostaglandins: Cyclooxygenase
j) Leukotrienes: Lipooxygenase
a) $PGD_2$: Vasodilatation
b) $PGF_{2\alpha}$: Luteolysis
c) Misoprostol; $PGE_1$ agonist
d) Dinoprostone: $PGE_2$ agonist
e) Carboprost: $PGF_{2\alpha}$ agonist
f) Gastric protection: $PGE_1$
g) Chemotaxis: $LTB_4$
h) Bronchial asthma: $LTC_4$
i) Montelukast: Leukotriene antagonist
j) Platelets: PAF
a) COX I inhibition: Gastric ulcer
b) COX II inhibition: Antiinflammatory
c) $PGF_{2\alpha}$ : Oestrus synchronization
d) $PGE_1$: Cytoprotection
e) Cytokine: TNFα
f) Platelet COX I: Aspirin
g) Inflammatory COX II: Meloxicam
h) Polypeptide: Substance P
i) ANF: Sodium excretion
j) H1 Blocker with antimuscarnic activity: Clemastine/Diphenhydramine/Methdilazine/Promethazine

# SECTION III: CNS PHARMACOLOGY

## Chapter – 13: TRANSMISSION IN CNS

### Chemical Mediators

The functional organization of the animal is regulated and coordinated by neurons in CNS. The function of the neurons, in turn, is via signalling mediated by chemical mediators (agonists). These mediators fall under three categories called neurotransmitters, neuromodulators and neurotrophic factors. Almost all the drugs acting on CNS produce their effects by modifying the prevailing function of central neurons through alteration of chemical signaling.

A **neurotransmitter** is a chemical synthesized, stored and released by presynaptic nerve terminals which acts rapidly on the membrane of postsynaptic neuron, producing a change in conductance of excitatory or inhibitory responses in the postsynaptic neuron. The neurotransmitters released from presynaptic nerve terminal produce rapid excitatory or inhibitory response on the postsynaptic neuron (dopamine, noradrenaline, acetylcholine, histamine, 5-hydroxytryptamine, glutamic acid, aspartic acid, GABA, glycine, purines).

A **neuromodulator** is a chemical that is formed *de novo* and released (not stored prior to release) by neurons as well as nonneuronal cells **(astrocytes),** having pre- or postsynaptic responses, modulating presynaptic neurotransmitter release or post-synaptic excitability (neuropeptides, nitric oxide, eicosanoids, anandamide, melatonin).

**Neurotrophic factors** are synthesised and released by nonneuronal cells and activate tyrosine-kinase-linked receptors which regulate gene expression and control nerve growth and phenotypic characters (cytokines, chemokines, growth factors).

The neurotransmitters are **amines** [acetylcholine, ACh; noradrenaline, NorA; Dopamine, DA; 5-hydroxy-tryptamine, 5-HT and Histamine, H] or **amino acids** [Excitatory: glutamic acid, GA and aspartic acid, AA; homocysteine (?); Inhibitory: gamma-amino butyric acid, GABA and glycine, GL]. A transmitter has either excitatory or inhibitory action or both on neurons depending upon the nature/type of nerves in brain or spinal cord.

### Noradrenaline

**Distribution:** Nonadrenergic neuron cell bodies are in pons and medulla from where the noradrenergic pathways extend to many parts of brain and spinal cord including cortex, cerebellum, hypothalamus, hippocampus, reticular formation, thalamus etc.

**Functions:** Control of wakefulness and alertness and mood. Functional deficiency leads to depression. Increase or decrease in central sympathetic tone and regulates the function of CVS, mainly the BP and cardiac function.

**Receptors:** G-protein-coupled Alpha and Beta adrenoceptors, activation of which results in excitatory or inhibitory effects.

**Agonists and Antagonists:** Adrenoceptor agonists and antagonists (see ANS).

### Dopamine

**Distribution:** Tuberohypophyseal system (Hypothalmus, median eminence and pituitary), mesolimbic and mesocortical pathways (midbrain, limbic system and frontal cortex) and mainly (about 80% of brain) in nigrostriatal pathway (substantia nigra, thalamus and corpus striatum).

**Functions:** Motor control, behavioural effects and endocrine function (control-prolactin secretion). Deficiency/degeneration of dopaminergic neurons causes Parkinson's disease in man.

**Receptors:** G-protein-coupled receptors (increase or decrease in cAMP). $D_1$, $D_2$ and $D_4$ (Cortex: arousal/mood); $D_1$to $D_5$ (Striatum: motor control); $D_1$, $D_2$, $D_3$ and $D_5$ (Limbic system: emotion and stereotype behaviour) and $D_2$ and $D_3$ (hypothalamus-anterior pituitary: prolactin secretion).

**Agonists:** Apomorphine and bromocriptine.
**Antagonists:** All receptors: Chlorpromazine, haloperidol and clozapine; $D_2$, $D_3$ and $D_4$: Spiperone and sulpiride.

**Acetylcholine**
**Distribution:** All parts of brain (forebrain, cortex, midbrain and brainstem).
**Functions:** Arousal, learning, memory and motor control. Degeneration of cholinergic neurons in hippocampus and basal forebrain results in Alzheimer's disease in man (loss of intellectual ability/dementia).
**Receptors:** Muscarinic receptors (presynaptic G-protein coupled) M1 in cortex and hippocampus, M4 in cortex and striatum, M5 in substantia nigra and M2 throughout CNS inhibit ACh release. Nicotinic receptors (pre- and postsynaptic inotropic). Subtypes $(\alpha4)_2$, $(\alpha7)_5$ and $(\beta2)_3$ in many areas of brain causing excitation.
**Agonists:** $(\alpha4)_2$ and $(\beta2)_3$: Nicotine, epibatidine, cytosine; $(\alpha7)_5$: Epibatidine and DMPP
**Antagonists:** $(\alpha4)_2$ and $(\beta2)_3$: Mecamylamine, methylaconitine and α-conotoxin; $(\alpha7)_5$ and: Methylaconitine and α-bungarotoxin.

**5-Hydroxytryptamine**
**Distribution:** Pons, medulla, cortex, limbic system, hypothalamus and spinal cord.
**Functions:** Hallucinatory behaviour, feeding behaviour, vomiting and control of mood/emotion, sleep/wakefulness and sensory pathways (including pain). $5\text{-HT}_{1D}$ agonists (sumatriptan, ergotamine, methysergide) are used as anti migraine drugs
**Receptors:** G-protein-coupled receptors:

| Receptor | Agonists | Antagonists |
|---|---|---|
| $5\text{-HT}_{1A}$ | Buspirone (partial) | Spiperone<br>Ergotamine (partial)<br>Methiothepin |
| $5\text{-HT}_{1B}$ | Ergotamine (partial) | Methiothepin |
| $5\text{-HT}_{1D}$ | Sumatriptan | Methiothepin<br>Ergotamine (partial) |
| $5\text{-HT}_{2A}$ | LSD<br>α-Methyl 5-HT | Ketanserin<br>Cyproheptadine<br>Methysergide |
| $5\text{-HT}_{2C}$ | LSD<br>α-Methyl 5-HT | Methysergide |
| $5\text{-HT}_3$ | 2-Methyl 5-HT<br>Chlorophenylbiguanide | Ondansetron<br>Tropisetron<br>Granisetron |
| $5\text{-HT}_4$ | Metoclopramide | Nil |
| $5\text{-HT}_5$ | Nil | Nil |
| $5\text{-HT}_6$ | Nil | All $5\text{-HT}_2$ antagonists |
| $5\text{-HT}_7$ | LSD | Nil |

**Histamine**
**Distribution:** Cell bodies in hypothalamus, with axons extend to all parts of brain.
**Functions:** Inhibitor of inhibitory transmitters (Arousal reaction) and mediation of central vomiting. $H_1$ antihistamines exert sedation.
**Receptors:** $H_1$ (postsynaptic excitatory), $H_2$ (postsynaptic inhibitory) and $H_3$ (presynaptic autoinhibitory). All are G-protein-coupled receptors.
**Agonists & Antagonists:** (See Autacoids)

**Glutamate/Aspartate**

**Distribution:** Glutamate in all parts of CNS (brain and spinal cord), but aspartate distribution is limited.

**Functions:** Fast excitatory transmission.

**Receptors:** NMDA (N-methyl-D-aspartate) postsynaptic slow EPSP, AMPA (Alpha-amino-3-hydroxy-5-hydroxy-5-methyl-4-isoxazolepropionate) postsynatic fast EPSP and kainate (isolated from a seaweed) pre and postsynaptic fast receptors (ionotropic); metabotropic pre and postsynaptic receptors (G-protein-coupled).

**Agonists:** NMDA on NMDA receptors, AMPA and Quisqualate on AMPA receptors; Kainate and domoate on kainate receptors; 1-aminocyclopemtate-1,3-dicarboxylic acid (ACPD) on metabotropic receptors. Polyamines (spermine and spermide) modulate NMDA receptor. Piracetam and aniracetam modulate AMPA receptor improve memory and cognitive performance (used in dementia)

**NMDA Antagonists:** Kynurenic acid and 7-chloro-kynurenic acid (require glycine also). Ketamine, dextromethorphan, phencyclidine, dizocilpine, remacemide and memantine antagonize glutamate action by blocking the channel.

**GABA**

**Distribution:** About one-third of synapses in brain. Formed from glutamate through decarboxylation by glutamic acid decarboxylase (GAD). It is degraded by GABA transaminase, Vigabatrine by inhibiting GABA transaminase counteracts epilepsy

**Functions:** Inhibition in all areas of CNS.

**Receptors:** $GABA_A$ (postsynaptic) and $GABA_B$ (pre and postsynaptic) which are ligand-gated chloride channel and G-protein-coupled receptors, respectively.

**Agonists:** GABA, diazepine (benzodiazepines), propofol and barbiturates and alphaxolone on $GABA_A$; GABA and baclofen on $GABA_B$

**Antagonists:** Bicuculline and flumazenil on $GABA_A$; phaclofen and saclofen on $GABA_B$

**Glycine**

**Distribution:** Grey matter of brain stem and spinal cord

**Functions:** Inhibitory transmitter in spinal neurons.

**Receptors:** Glycine (postsynaptic) receptor like $GABA_A$ receptor a ligand-gated chloride channel.

**Agonists:** Glycine

**Antagonists:** Strychnine. Tetanus toxin prevents its release.

Adenosine safety mech

ATP = ADP + Adenosine cause platelet aggregation

**Purines**

**ATP and Adenosine (Neurotransmitters and/or neuromodulators)**

**Distribution:** CNS (and peripherally also) in purinergic nerves.

**Function:** ATP as transmitter or modulator and adenosine as a widespread modulator. Adenosine may act as a protector of central neurons against damage caused due ischaemia or over stimulation (safety mechanism). Adenosine causes CNS depression (drowsiness, motor incoordination, analgesia and anticonvulsant actions). ATP is released during tissue injury, acts as one of the mediators of pain sensation (nociception). Released ATP is converted to ADP and adenosine. ADP causes platelet aggregation and dilatation of vascular smooth muscle, pre and postsynaptic depression (CNS).

**Receptors:** $A_1$, $A_2$ and $A_3$ (G-protein-coupled) receptors for adenosine and ATP acts on ligand-gated cation channel $P_{2X}$ excitatory receptors and G-protein-coupled $P_{2Y}$ inhibitory receptors

**Agonists:** ATP and adenosine on respective receptors.

**Antagonists:** Caffeine overcomes drowsiness (arousal reaction and alertness) is an antagonist of $A_2$ receptors.

Pain Sensation (Nociception)

**Nitric Oxide (NO):** It is mainly a chemical mediator of peripheral tissues, but also found in some areas in CNS (cerebellum and hipocampus), synthesized by a neuronal constitutive enzyme nitric oxide synthetase (nNOS). It produces its effects by activation of guanylate cyclase to increase cGMP formation. It also forms a potent toxic anion peroxynitrite ($ONOO^-$) by reacting with superoxide free radical ($O_2^-$). The peroxynitrite anion causes oxidative damage of many intracellular proteins and may cause brain ischaemia. (**CO** may also serve as a modular function in CNS like NO. Also acts like NO in promoting cGMP formation).

**Opioid Peptides**

These are protein in nature and endogenous, named so because of their actions and effects similar to opiates, the opium analgesics, of which morphine is the principal alkaloid. The opioid receptors, their agonists and location are as listed below:

| Criteria | Oipoid Peptides | | | |
|---|---|---|---|---|
| | B-Endorphin | Enkephalins | | Dynorphin |
| | | Leucine | Methionine | |
| Receptors | μ, δ and κ | μ and δ | μ and δ - | μ, δ and κ |
| Location | Peripheral & CNS | Spinal | Spinal | Peripheral & CNS |

The opioid peptides exert their analgesic effect through activation of G-protein-coupled receptors that have inhibitory influence ($G_i$) on adenyl cyclase and G-protein receptors linked to ion channels opening $K^+$ channels and inhibition of opening of $Ca^{++}$ channels causing hyperpolarization and inhibition of release of pain inducers also. The oipoid receptors get activated (or increase in number) due to pain in inflammatory process. The pain sensation is subsided with the release and action of opioid peptides (CNS and peripheral)

**Tachykinins:** Include substance P (SP) and neurokinin A (NKA) and neurokinin B (NKB). Widely distributed in CNS; whereas, SP and NKA are in peripheral sensory nerves, facilitating nociception and and mediating the local inflammatory responses.

**Melatonin:** It is the hormone of pineal gland formed from 5-HT. It is responsible in establishing circadian rhythms. Its secretion is influenced by light intensity (high in night and low in day) which is regulated by the hypothalamus through retinohypothalamic sympathetic (NorA) nerves. It acts through melatonin receptors (G-protein-coupled) found in retina and hypothalamus. The hormone has been claimed to be value to overcome 'jet lag' or in increasing the performance of night-shift workers. When given during day-time it induces sleep.

**Lipid Mediators:** The formation of eicosanoid metabolites of arachidonic acid through cyclooxygenase and lipoxygenase pathways (prostaglandins, leukotrienes and HETEs) also occurs in CNS. These may also serve as intraneuronal messengers and also diffuse out of the nerve cell and produce effects on presynaptic nerve terminals or neighbouring cells by activating intracellular or extracellular receptors.

The functional integrity of the nervous system in regulating the physiological activity of an individual is the result of interplay of the central neurochemicals (above). Degeneration of central neurons and/or absence of central neurotransmitters results in neuro-degenerative disorders in human beings as listed below:

| Disease | Cause | Symptoms |
|---|---|---|
| Parkinson's Disease | Imbalance between dopamine and ACh in nitrogastrial tract | Disorder of movement in old. Tremor at rest. |
| Alzheimer's Disease | Loss of cholinergic neurons. | Loss of intellectual ability with age (dementia). |
| Schizophrenia | Excess dopaminergic neuron activity. | Thought disorders, delusions, hallucinations and social withdrawal. |
| Huntington's Disease (Heriditary) | Excess dopaminergic activity and loss of GABA inhibition. | Sudden jerky involuntary movements. |

Therapy of Parkinson's disease (PD) should be aimed at decreasing ACh level/activity to correlate lowered dopamine levels or by increasing dopaminergic activity to correlate normal ACh levels. The drugs used in PD are:

**Selegiline**: Inhibits $MAO_B$ (selectively degrades dopamine) and increases dopamine in substantia nigra and thus corrects dopamine/ACh ratio.

**Tolcapone**: Inhibits COMT and increases absorption of L-Dopa and thus the formation of dopamine in brain (COMT metabolizes L-Dopa before its absorption).

**Amantadine**: An antiviral drug with antiparkinsonian effect. It acts by increasing dopamine levels and exerting anticholinergic effects in normalizing dopamine/ACh ratio.

**Biperidin, procyclidine, benztropine and trihexyphenidyl**: These are **antimuscarinic drugs** help in lowering muscular rigidity and tremor in PD.

**Alzheimer's Disease** signs can be corrected by **AChE inhibitors rivastigmine and donepezil** (have more affinity for AChE in CNS than peripheral ChEs). These drugs improve cognition and memoray by increasing ACh levels in cerebral cortex and limbic system

# Chapter – 14: GENERAL ANAESTHETICS - INTRODUCTION

## 1. Historical Background

The first anaesthetic, nitrous oxide gas (laughing gas) was discovered by Priestly in 1776. It was first used as an anaesthetic by a dentist Horace Wells (Hartford, USA) in 1844 for removal of a tooth in a human patient. Sir Humphry Davy (British chemist) suggested its use in painless surgery. Anaesthetic effect of ether was discovered by C W Long in 1818. Ether anaesthesia was first publicly demonstrated in 'Ether Dome' by William T G Morton in Massachusetts General Hospital (Boston, USA) in the year 1846. Oliver Wendell Holmes coined the term Anaesthesia in 1846. Chloroform anaesthesia was introduced by James Young Simpson (Scottish obstetrician) in 1847. Chloral hydrate was the first intravenous anaesthetic used (1872). Barbiturates were introduced in 1903. Cyclopropane was discovered in 1929. Thiopentone was introduced as general anaesthetic in 1935.

Anaesthetics cause anaesthesia meaning loss of sensations (mainly pain) resulting from reversible depression of function of nerves. The purpose of anaesthesia is to perform painless surgery. Anaesthesia can be achieved by either systemic (general anaesthesia) or local (local or regional anaesthesia) administration.

## 2. Definitions

**General Anaesthesia**: Reversible loss of sensations of whole body accompanied by reversible loss of consciousness.

**Regional Anaesthesia**: Reversible loss of sensations of a large portion/area of the body (pelvic or abdominal region) without affecting the consciousness.

**Local Anaesthesia**: Reversible loss of sensation of a particular limited/small area of the body (eye, horn base, limbs or flank).

General anaesthesia is generally employed in small animal surgery, but not usually recommended in large animals. Large animals are considered unfit for general anaesthesia [(animal is recumbent, the voluminous rumen/stomach contents may enter respiratory tract due to regurgitation and the distended rumen (accumulation of gases) presses on diaphragm causing respiratory distress and the vena cava reducing venous return resulting in reduced cardiac out put (cardiaovascucular insufficiency)].

**Surgical Anaesthesia**: A state of anaesthesia under which the animal is in normal deep sleep, without responding to painful stimuli, and surgical operations can be carried out without causing pain to the animal.

**Balanced Anaesthesia**: It is safe general anaesthesia ensuring satisfactory loss of pain sensation, motor reflexes, mental activities and adequate muscle relaxation achieved by proper preanaesthetic medication, where the induction of anaesthesia and recovery from anaesthetic depression are smooth without any complications.

**Basal Anaesthesia**: Lighter level of anaesthsia produced by preanaesthetic depressants, where the animal may become unconscious, but is not sufficiently depressed for painless surgery.

**Administration of General Anaesthetics**: By Inhalation and IV routes commonly. In ferocious/vicious, wild or uncooperative animals by IM or IP routes. Inhalation anesthesia requires special equipment like Boyles apparatus, masks, intubation tubes etc., but IV anaesthesia requires only a hypodermic syringe and a needle.

**Ideal General Anaesthetic: Desirable Properties of a General Anaesthetic:**

a. Wide margin of safety: Anaesthetic doses should not unduly depress the vital medullary respiratory and cardiovascular centres.
b. Smooth and rapid induction followed by quick and smooth recovery.

c. Adequate skeletal muscle relaxation.
d. Nontoxic to vital organs of the body (heart, lung, kidney and liver)
e. Should not promote capillary bleeding during surgery.
f. Rapidly excreted, and not present in edible tissues (meat and eggs) or milk.
g. Stable and nonexplosive during storage and
h. Economical and easily available.

**3. Theories of General Anaesthesia**: (Mode of action)

a. **Lipid Solubility Theory of Overton and Meyer (1901)**: Compounds with high lipid solubility easily penetrate the CNS, being rich in lipids, and alter the function of nerves. Potency of an anaesthetic is directly proportional to its affinity and solubility in lipid portion of the nerves. This theory correlates potency of an anaesthetic to its lipid solubility

k) **Surface Tension or Adsorption Theory of Traube (1904)**: The anesthetic potency is correlated to the ability of the agent to reduce the surface tension of the neuronal membrane by adsorption. Thus the anesthetic agent alters the transmembrane ionic permeabilities across the neuronal membrane and interefere with nerve function (generation of action potential: NAP).

l) **Microcrystal Theory of Pauling and Miller (1961)**: Anaesthetics facilitate formation of microcrystals or icebergs/clathrates: ice crystals within the nerve cells and thus disrupt conductance of impulses.

m) **Protein Binding Theory of Frank and Lieb (1982)**: Anaesthetics act by reversibly binding to a hydrophobic domain of a protein or by concentrating at the lipid-protein interface in the nerve cell membrane. The binding causes expansion of the nerve membrane and thus interferes with the function of nerve membrane proteins..

n) **Receptor Theory**: By interacting with the neurotransmitter receptors (as agonists of inhibitory transmitters or antagonist of excitatory transmitters) in the CNS. Anaesthetics either inhibit the receptors of excitatory transmitters glutamate, ACh and 5-HT, or enhance the function of receptors (agonists) of inhibitory transmitters (GABA and glycine).

o) **Ion Channel Theory**: Anaesthetics bind to voltage-gated ion channels and reduce excitability or promote inhibition of nerve membrane.

**4. Stages of Anaesthesia**

Clinical response of the animal to the administration of an inhalation anaesthetic is divided into four stages in order to assess the level of CNS depression. The level of depression progresses in the order of cerebral cortex through midbrain, spinal cord and finally the medulla.

Stage I: Voluntary Movement or Excitement (Stage of Analgesia)
Stage II: Involuntary Movement or Excitement (Delirium)
Stage III: Surgical Anaesthesia: Planes 1 & 2: Light Surgical Anaesthesia
Planes 3 & 4: Deep Surgical Anaesthesia
Stage IV: Medullary Paralysis

**Stage I**: This stage starts from the beginning of anaesthetic inhalation and lasts up to the loss of consciousness. The animal struggles to avoid inhaling strange and unpleasant anaesthetic vapours. There is release of adrenaline due to fear and excitement. Sensory cortex is depressed. Respiration is rapid and irregular, with rise in BP and pulse rate. All sensory reflexes are present.

**Stage II**: This stage starts from loss of consciousness to beginning of regular respiration. The animal gradually looses consciousness and reacts to external stimuli with reflex struggling or movements (limbs with pedal or galloping movements). Reflex vomition occurs in dogs unless feed is withheld for 6 hr or more prior to anaesthesia. Nystagmus is seen in horses. Depression extends to motor cortex. Respiration is very irregular with rise in BP and pulse rate. All sensory reflexes are present.
The stages I and II are collectively comprise Induction of Anaesthesia.

**Stage III**: This stage extends from onset of regular respiration to cessation of spontaneous breathing.Depression is extended from cortex and mid brain to spinal cord. It is divided into 4 planes:

Planes 1 and 2: Light surgical anaesthesia and Planes 3 and 4: Deep surgical anaesthesia.
In Plane 1 the depression is extended to mid brain and spinal cord partly, with slow and regular respiration, normal BP and pulse rate and presence of all neuromuscular (NM) reflexes.
In Plane 2 the depression covers all spinal cord, with slow and regular respiration, normal BP and pulse rate and absence of eye lid, skin, swallowing (pharyngeal), pedal and photomotor reflexes. The corneal and cough reflexes are present.Presence of cough reflex prevents entry tissue devris into respiratory tract during during pharyngeal surgery. When muscle relaxants are used as preanaesthetics, the level of anaesthesia is assessed by noting the photomotor reflex. **Most of the surgical operations are done in Plane 2 of Stage III.**

The animal is not generally allowed to pass into deep surgical anaesthesia, where there is marked depression of respiration and CV functions accompanied by hypothermia due to depression of hypothalamic thermoregulatory centre.
In Plane 3 the depression covers whole of spinal cord, with thoracic or abdominal respiration, fall in BP and rapid and weak pulse and absence of all the reflexes; pupil starts dilating.
In Plane 4 the depression extends to part of medulla with shallow abdominal respiration (intercostals paralysis), fall in BP and rapid and weak pulse, dilated pupil and absence of all NM reflexes.

**Stage IV**: This stage starts from cessation of breathing and extends till cardiovascular failure and death. The stage is called stage of medullary paralysis where the vital medullary centres are paralysed with cessation of respiration, severe fall in BP, feeble pulse and absence of all NM reflexes and animal dies unless urgent revival measures (artificial respiration, administration of analeptics and CV stimulants) to counter excess CNS depression are not instituted at once.
The above stages can be demonstrated with somewhat clear cut distinction during inhalation anaesthesia, but not with intravenous anaesthesia, where the animal very rapidly goes into surgical anaesthesia.

**Classification of General Anaesthetics**: Based on route of administration:

**I. Inhalation Anaesthetics**: Two groups basing on physical properties :

- **A. Volatile Anaesthetics**: Ether, halothane, methoxyflurane, enflurane, isoflurane, chloroform etc.
- **B. Gaseous Anaesthetics**: Nitrous oxide and cyclopropane

**II. Parenteral Anaesthetics** (mostly intravenous route): Barbiturates, chloral hydrate, magnesium sulfate, chloralose, urethane, ketamine, phencyclidine, althesin, etomidate, metomidate, propofol, propanidid etc.

# Chapter – 15: INHALATION ANAESTHETICS

## 1. Major Volatile Anasthetics

| Parameter | Ether | Halothane | Methoxyflurane |
|---|---|---|---|
| **Properties** | Characteristic odour and sweetish taste. Oxidizes to peroxides (irritate resp. tract ) upon exposure to moisture. | Characteristic sweetish odour. Decomposes upon exposure to sunlight (0.10% thymol is added as preservative). | Characteristic pungent odour. Decomposes upon exposure to light. Butylated hydroxytoulene is added as preservative. |
| MAC (%) | 3. Least potent. Slow induction | 0.75-1.20. Induction 3-5 min. | 0.23. Slow induction(10 min) |
| CNS | All stages are seen | Stage II bypassed | Stage II bypassed |
| CVS | Induction– release of adrenaline: increase in heart rate & BP. Stage III: Fall in BP and COP (depression of VM centre). Does not sensitize heart to catecholamines | Direct myocardial depression (reducing intracellular $Ca^{++}$). Sensitizes heart to catecholamines (arrhythmia) | No change in heart rate or mild tachycardia. Adrenaline can induce cardiac arrhythmia. |
| Respiration | Initial stimulation followed by progressive depression. Increase bronchial secretion | Depression with increase in duration of anaesthesia, may develop acidosis. | Initial stimulation followed by progressive depression with increase in anaesthesia. |
| SK. Muscle relaxation | Sig. effect. Dose of dTC to be reduced to one-third | Low to satisfactory relaxation. dTC can be used if needed. | Adequate relaxation. dTC can be used if needed. |
| Liver | Prolonged anaesthesia lowers liver glycogen. Not hepatotoxic | Hepatotoxic like chloroform | No significant effect |
| Kidney | Long duration : oliguria/ anuria due to ADH release | No significant effect | No significant effect |
| Body Temp-erature | Hypothermia | Malignant hyperthermia in pig and horse (persistent muscle contraction due release of $Ca^{++}$ from sarcoplasmic reticulum) and hypothermia in others | Hypothermia |
| Foetus & Uterus | No significant effect | Reduce uterine contractions. Neutralizes oxytocin. Readily crosses placenta. | Reduces uterine contractions,neutralizes oxytocin. Readily crosses placenta |
| GIT | Nausea & vomition common during induction or recovery | No vomition during induction or recovery | Nausea & vomition during induction or recovery |
| Merits | Safest in small animals with proper premedication. Ready control of anaesthesia. Good analgesia, muscle relaxation. Cheap. Ready control of anaesthesia. No costly equipment is needed. | Potent; used in small or large animals; rapid induction (3-5 min) & recovery (10-15 min); nonirritant, ready control of anaesthesia (low blood solubility), nonflammable & nonexplosive | Most potent. Can be used in small or large animals. Excellent muscle relaxation and analgesia. Nonflammable. |

| | | | |
|---|---|---|---|
| Demerits | Highly flammable. Difficult to use in hot climate. Irritant to resp. tract. Delayed induction without proper premedication | Resp. and cardiac depression and poor muscle relaxation and analgesia. Malignant hyperthermia in pig and horse. Expensive (requires closed circuit apparatus) | Easy control of anaesthsia not possible (high blood solubility). Recovery prolonged. Poor vaporization. Needs close circuit apparatus |
| Contra-indications | Aminoglycoside antibiotics (synergistic curariform effect) | Aminoglycoside antibiotics (synergistic curariform effect), catecholammines and Ca channel blockers. CHF | Noradrenaline or epinephroine without premedication. |
| Uses | Not used in human or vety. surgery. Main use in lab animals for surgery or euthanasia | Used in small and large (horse) animals, mainly for maintenance (2-8 ml/45 kg/hr) of anaesthesia with $NO_2$, after induction by ultrashort acting barbiturate. | Used in small or large animal surgery for induction (3% MF+$N_2O$(70%)+$O_2$(27%) and maintenance (2-3%) |

**MAC** is the minimum alveolar concentration; the lowest concentration of the inhalant anaesthetic in pulmonary alveoli in producing immobility due to surgical incision in 50% of the individuals. It is the measure of potency of inhalation anaesthetics.

## 2. Other Volatile Anaesthetics

**Enflurane**: A colorless, pungent, nonflammable volatile liquid, chemically related to methoxyflurane. The most frequently used potent anaesthetic in human surgery.It is classified as a convulsive anaesthetic (epilepsy like seizures; dissociative-cataleptic anaesthesia). Its MAC for horse is 2.12%. It causes CNS excitation in dogs causing muscular twitchings (face, neck, limb and abdomen) if diazepam preanaesthesia is not given. In comparison to halothane this does not sensitize heart to catecholamines and has more depressant action on respiration and better muscle relaxatiion

**Isoflurane**: Though an isomer of enflurane does not cause CNS excitation. It is about one and half times more potent than enflurane, MAC 1.3%). It provides satisfactory skeletal muscle relaxation (synergistic neuromuscular blockade with curariform agents).

**Chloroform**: It is replaced by other safer anaesthetics, sometimes used for euthanasia. Its use is associated with risk of death of the animal during induction, prolonged anaesthesia and during post-anaesthetic period. During induction majority of deaths occur due to direct toxic effect on heart. During Stage I the animal tries to avoid inhaling chloroform vapours by temporary breath-holding, which is followed by reflex deep breathing taking a high concentration of chloroform vapours into lungs, from there through pulmonary veins into the heart, causing ventricular fibrillation and/or cardiac arrest. Cardiac toxicity may be avoided by proper premedication (sedatives) and slow administration of chloroform. Prolonged surgical anaesthesia may cause respiratory failure due depression of medullary respiratory centre. Post-anaesthetic toxicity is due to degenerative changes in liver, kidney and heart (delayed chloroform poisoning i.e. 24 to 48 hr after anaesthesia). Following prolonged exposure to air and light chloroform gets oxidized to phosgene gas (a marked lung irritant). Phosgene formation is prevented by adding ethyl alcohol @ 1 per cent.

## 3. Anaesthetic Gases

**Nitrous Oxide** ($N_2O$; Laughing gas): It is discovered by Joseph Priestly (1772). It is a colorless, nonirritating and nonflammable gas. It is a nonflammable and noirritating gas. It causes excitement, delirium and amnesia in humans, hence the name laughing gas. Has very low anaesthetic potency (MAC: 188 (cat) 255 (dog) %) and hence must be combined with other inhalation anaesthetics (halothane or methoxyflurone). It has good analgesic, but poor muscle relaxant effects. To avoid hypoxia it is used in combination with oxygen (nitrous oxide 70%:oxygen 25%) and other inhalation anaesthetic (0.2 – 2%).

**Cyclopropane**: Colorless gas with a characteristic odour. It can be used in small animal surgery of short duration after diluting with oxygen (4 times) through a closed circuit system. Morphine premedication and catechloamines are contraindicated due to marked respiratory depression and cardiac arrhythmia respectively. It causes adequate skeletal muscle relaxation. It forms flammable mixture with air.

chloral hydrate was first intravenous Anaesthetic

# Chapter – 16: INTRAVENOUS ANAESTHETICS

**Advantages of Intravenous Anaesthesia:**

a. Easy, rapid and smooth induction of anaesthesia
b. Smooth recovery with no complications as seen in inhalation anaesthesia
c. Vomtion absent during induction
d. No interference in operations of head region
e. Minimum equipment is required
f. Can be used with thermocautery and diathermy
g. Respiratory complications are not aggravated
h. Surgeon alone can manage anaesthesia and perform surgery

**Disadvantages of Intravenous Anaesthesia:**

1. Level of anaesthesia not readily controllable
2. No adequate skeletal muscle relaxation
3. Contraindicated in hepatic and renal diseases
4. Unsuitable ( barbiturates) for cesaerean section (depression of foetal respiration)

## 1. Barbiturates

**Chemistry**: Derivatives of malonyl urea (2,4,6-trioxohexahydropyrimidine), a conden-sation product of urea and malonic acid. It was first synthesized by Conrad and Gutzeit in 1882. Fischer and von Mering prepared diethyl barbituric acid and discovered its hypnotic activity. They named it as Veronal from the Latin *vera* (true) having real hypnotic effect. Baeyer named malonylurea as barbituric acid, which formed the key molecule for a series of hypnotics, was prepared on Saint Barbara's feast day.

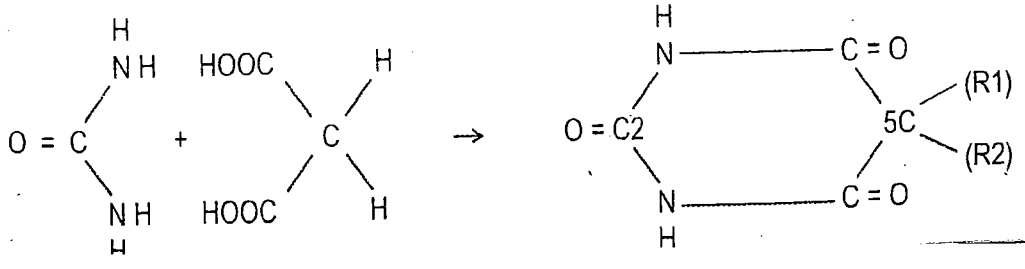
**Classification:** Based on duration of anaesthesia:

| CATEGORY (DURATION) | EXAMPLES | SUBSTITUTION AT | | |
|---|---|---|---|---|
| | | C2 | C5 | |
| | | | R1 | R2 |
| Long acting (4 – 6 hr) | Barbitone | O | Ethyl ($C_2H_5$) | Ethyl ($C_2H_5$) |
| | Phenobarbitone | O | Ethyl ($C_2H_5$) | Phenyl ($C_6H_5$) |
| Intermediate acting (2– 4hr) | Pentobarbitone | O | Ethyl ($C_2H_5$) | 1-methylbutyl ($CH(CH_3)$-$CH_2$-$CH_2$-$CH_3$) |
| | Butobarbitone | O | Ethyl ($C_2H_5$) | Butyl ($CH_2$-$CH_2$-$CH_2$-$CH_3$) |
| Short acting(1–2 hr) | Secobarbitone | O | Allyl ($C_3H_5$) | 1-methylbutyl ($CH(CH_3)$-$CH_2$-$CH_2$-$CH_3$) |
| Ultra short acting (20-40min) | Thiopentone | S | Ethyl ($C_2H_5$) | 1-methylbutyl ($CH(CH_3)$-$CH_2$-$CH_2$-$CH_3$) |
| | Thiamylal | S | Allyl ($C_3H_5$) | 1-methylbutyl ($CH(CH_3)$-$CH_2$-$CH_2$-$CH_3$) |

**Structure Activity Relationship:**

1. Barbituric acid (pyrimidine nucleus) is devoid of CNS depressant activity; substitution of alkyl or allyl groups at C5 (R1 and R2) results in sedative-hypnotic-anaesthetic effects.
2. Short chain substitution at R1 and R2 resists oxidation resulting in long duration of action.
3. Long chain substitution at R1 and R2 promotes oxidation resulting in reduction in duration of action.
4. Replacement of carbonyl oxygen at C2 by sulfur atom makes the compounds highly vulnerable to oxidative metabolism rendering the compounds very short acting.
5. Replacement of carbonyl oxygen at C2 by an HN= group (guanidine derivative) destroys CNS depressant activity.
6. The substitutions at C5 should not be less than 4 and not more than 8 for optimal CNS depression. Substitution with long chain having more than 9 carbon atoms makes the compound convulsant.

**UREA + MALONIC ACID → MALONYLUREA (BARBITURIC ACID)**



**Mechanism of Anaesthetic Action:**

1. Enhancement of central inhibitory processes mediated by GABA (benzodiazepine receptor $Cl^-$ channel complex) at interneuronal sites in brain and presynaptoc sites in spinal cord. Has both GABA facilitatory as well as GABA mimetic action (direct increase in $Cl^-$ conductance). Barbiturates bind to barbiturate receptor on the Cl-channel in excitable neuronal cells. Activation of the receptor increases Cl-influx across the neuronal membrane causing partial hyperpolarization of the neuronal membrane and decreased conductance. Since the barbiturate is adjacent to both benzodiazepine and GABA receptors on the Cl-channel, barbiturates not only modulate binding of GABA to its receptor and also the benzodiazepines to benzodiazepine receptor.
2. Antagonism of calcium ion in releasing release of excitatory neurotransmitter glutamate and other transmitters in CNS (ACh and noradrenaline).
3. At high doses also depress $Na^+$ and $K^+$ permeability across nerve membrane.

**Major Pharmacological Effects**:

A. **CNS:** Dose-dependent depression: Mild sedation to deep hypnosis and surgical anaesthesia. Depress both sensory and motor cortex.
B. **Resp. System**: Slight depression at anaesthetic dose, but respiration failure at high dose (depression of medullary respiratory centre).
C. **CVS**: Rapid IV injection causes sharp, but transient fall in BP. High doses cause prolonged fall in BP (due to vasodilatation and depression of vasomotor centre and heart).
D. **Kidney**: No significant effect at anaesthetic dose, but high doses cause oliguria/anuria (reduced renal blood flow: CVS effect).
E. **Uterus and Foetus**: Anaesthetic doses depress parturient uterine contractions. Also cross placenta cause depression of foetal respiration and death of foetus *in utero*.
F. **Skeletal Muscles**: No relaxation.
G. **Smooth Muscles**: No significant effect, except in GIT where tone and motility are slightly reduced.

**Pharmacokinetics**: Barbiturates are readily absorbed from GIT (faster for short acting and slower for long acting). They are widely distributed in the body. The rate of entry of barbiturates into CNS depends on their lipid solubility (high lipid soluble thiopentone has fast entry, while less lipid soluble phenobarbitone enters very slowly). Plasma protein binding varies with compound (thiopentone 75% and phenobarbitone 20%). Barbiturates readily cross placenta and enter fetus and also are secreted in milk. The actions of barbiturates are terminated by three processes: redistribution (high lipid soluble thiopentone), hepatic microsomal metabolism (drugs with intermediate lipid solubility: short acting) and renal excretion (drugs with low lipid solubility: long acting). Barbiturates induce hepatic microsomal enzymes and thereby increase the rate of their own metabolism and other drugs.

**Therapeutic Uses**:

1) As sedatives and hypnotics
2) As IV general anaesthetics
3) As anticonvulsants (antiepileptics)
4) For euthanasia

**Toxicity**: High doses cause death due to respiratory failure followed by cardiac arrest. Patient can be revived by artificial respiration or giving analeptics as long as heart continues to beat.

**Doses for IV anaesthesia (mg/kg)**: **Thiopentone** (most commonly used, Pentothal/Intraval): Cat and dog: 20-25; Pig: 10-12; Calf/goat: 15-20; Horse: 10. It is administered as 2.5% solution in small animals and as 5-10% aqueous solution in large animals. (**Note**: Half of the total calculated dose is injected rapidly and the reminder slowly by observing the level of anaesthesia. Should not be injected SC or IM due to marked tissue irritation and should not be allowed to leak into perivascular spaces while injecting iv).

**Pentobarbitone sodium** (Nembutal): As anaesthetic: Dog or Cat: 25-30 mg/kg IV (3-6% aqueous solution).

**Thiamylal sodium**: For induction of anaesthesia: Dog: 15-20 mg/kg for induction (4% aqueous solution) following premedication with atropine and morphine.

## 2. Chloral Hydrate (CH):

CH ($CCl_3CH(OH)_2$)has low margin of safety (depresses respiratory and vasomotor centres at anaesthetic doses). Has poor analgesic effect, but has satisfactory hypnotic effect. Ninety-five per cent of CH is reduced in liver to trichloroethanol (active metabolite: hypnotic effect) after oral administration. As it causes gastric irritation it needs to be administered after adequate dilution with water. Due to AntiChE property CH antagonizes the curariform effect on skeletal muscles (relaxation). It is commonly used as a preanaesthetic (general/local or regional anaesthesia), sedative or hypnotic in large animals (10 to 20 gm/adult animal as 7% aqueous solution IV, about 125 – 200 ml or 5 gm/45 kg orally in about one liter warm water through stomach tube). Hypnosis occurs within 10 – 20 min. CH is rarely used in small animals.

**Chloral hydrate + Magnesium sulfate (Chlormag anaesthesia)**:

As iv anaesthesia in large animals: Curariform effect of Mag. Sulf and hypnotic effect of CH serve as a satisfactory anaesthetic combination. The combination is used as 300 to 400 ml of 12% CH and 6% mag. sulfate in horses and cattle and 12% of both in camels.as aqueous solution by slow I/V injection till satisfactory effect. The solution must be used within one hr, discard in case of any turbidity.

**Chloral hydrate + Magnesium sulfate + Pentobarbitone (Chlorpent anaesthesia)**:

Produces satisfactory anaesthsia without the toxic effects of individual drugs following slow iv injection of aqueous solution containing 3 % CH, 1.5 % mag.sulf and 0.66 % pentobarbitone @ 500 to 750 ml in large animals (till satisfactory effect). In birds aqueous propylene glycol with 9.5% alcohol containing 20 gm CH, 10 gm mag. sulfate and 5 gm pentobarbitone per 500 ml is used as anaesthetic. Dose: I/M injection (pectoral muscles) @ 0.2 to 0.25 ml / 100 G body weight (till effect).

## 3. Dissociative Anaesthetics

These produce dissociative anaesthesia characterized by marked sensory loss, analgesia, amnesia, paralysis of movement without loss of consciousness, but increase in skeletal muscle tone (catalepsy : cataleptoid anaesthesia). However, the patient is completely dissociated from the environment (unaware of the surroundings).

Ketamine, phencyclidine and tiletamine are the dissociative anaesthetics which act as antagonists of excitatory amino acid glutamate (at NMDA type glutamate receptor) and interfere with neuronal transport of 5-HT, dopamine and noradrenaline in CNS. Act on cerebral cortex. At anaesthetic doses no significant effect on respiration, but increase BP and heart rate due to sympathetic stimulation (can be used in patients in CV shock). Preanaesthetic diazepam, acepromazine or xylazine administration is necessary before dissociative anaesthsia.

**Ketamine**:

Dog: Anaesthesia: 10mg/kg IV after diazepam (0.5mg/kg IV). Restraining: 10-15mg/kg + acepromazine (0.25mg/kg I/M)

Horse: 2mg/kg IV in combination with diazepam (0.2mg/kg IM) and xylazine (1mg/kg IV).

Cattle: Induction: 2 mg/kg rapid IV or IV; Maintenance: 0.2% ketamine in normal saline solution administered @ 10 ml/min.

Goat: 10 mg/Kg IV 10 min after xylazine (0.2 mg/kg IM). If further anaesthesia is needed ketamine @ 6 mg/kg IM.

**Phencyclidine**: Effect on CNS is species specific. Depression in dog and in other species depression in low doses and excitation/convulsions in high doses. In combination with other drugs it is primarily used in subhuman primates:

Monkey: 1.5 mg/kg IM followed by 4-10 min pentobarbitone @ 5 mg/kg IV.

**Tiletamine**: It is available in combination with zolazepam (tranquilizer). In cat and dog the combination @ 6-13 mg/kg IM and @ 3 mg/kg IM in nonhuman primates produces satisfactory anaesthesia

## 4. Other Parenteral Anaesthetics

**Althesin**: A steroidal anaesthetic generally used for induction of anaesthesia. It contains two pregnanediones, alphaxalone (steroid I) and alphadolone acetate (steroid II). Produces rapid induction of short duration anaesthesia followed by smooth recovery.

Cat: Induction of anaesthesis @ 9 mg/kg IV (anaesthesia 10 – 12 min). For sedation 9 mg/kg IM.
Birds: 10-14 mg/kg IV
Sheep: Induction @ 3 mg/kg IV, for maintenance infusion of its dilute sol @ 0.234 mg/kg/min.
Swine: Sedation 1-9 mg/kg IM (neck muscles).
Contraindications: Not used in dogs, because the vehicle surfectant (cremophor EL) in the preparation causes histamine release resulting in CV shock in this species. It should not used with barbiturates.

**Propofol**: It is an oily liquid introduced as 1% emulsion for IV induction and short duration anaesthesia. Its anaesthesia is followed by quick recovery (rapidly metabolized). Dose in man: 2 mg/kg.
**Etomidate**: Has potent hypnotic effect, but no analgesic effect. Causes rapid induction of anaesthesia. Has wide margin of safety. Dog @ 1.5 to 3 mg/kg IV
**Metomidate**: Birds: 8.8 to 16 mg/kg IM (leg muscles)
All the above three drugs induce rapid anaesthesia and are more quickly metabolized than barbiturates. Wide margin of safety (No hangover like thiopentone so preferred in humans). It is recommended for anaesthesia in birds.
**Urethane**: Also called ethyl carbamate. Chemically related to urea. Commonly used in lab animals. Rat: @ 1 gm /kg IP; Rabbit : @ 1.6 gm/kg IP or 1.75 gm/kg SC. Not used clinically. Anaesthesia lasts for hours.
**Chloralose**: A condensation product of chloral hydrate and glucose. It is metabolized to chloraldehyde and then to trichlorethanol. Produces dissociative anaesthesia like ketamine. Dog :@ 40-100 mg/kg IV. Anaesthesia lasts for 6 – 10 hr.
**Midazolam:** A benzodiazepine derivative with slower onset of anaesthetic action, but has no respiratory or cardiovascular depressant effect. In humans it is generally used as a preoperative sedative for endoscopy or other probing procedures.

## 5. Preanaesthetic Medication (Premedication)

Balanced/safe anaesthesia is ensured by proper premedication i.e. administration of specific drugs before inducing anaesthesia.
**Objectives of Premedication**:
a. Restraint of uncooperative, ferocious or excited animal
b. Smooth and rapid induction followed by smooth recovery.
c. Reduce dose of anaesthetic and minimize toxicity.
d. To supplement analgesic action of anaesthesia.
e. Control salivary and bronchial secretions (especially with inhalant anaesthetics)
f. Prevent cardiac arrest (due to reflex vagal stimulation).
g. To produce adequate skeletal muscle relaxation.
*h.* To prevent vomition during induction or recovery.
*i.* Before GI surgery to empty and sterilize the GIT

**Preanathetics, their Doses and Administration**:
**For objectives a, b, c and d**:
**Acepromazine**: Dog & Cat (0.05-0.1 mg/kg IM/IV); Pig (0.1-0.2 mg/kg IV); Horse (0.02-0.04 mg/kg IV)
**Butorphanol**: Dog (0.05-0.1 mg/kg IM)
**Chlorpromazine**: All species (0.5-2.0 mg/kg IM)
**Diazepam**: Dog (0.2-0.5 mg/kg IM); Pig (0.5 mg/kg IV); Horse (0.05 mg/kg IV)
**Meperidine**: Dog (5-10 mg/kg IM) Cat (2-4 mg/kg IM); Pig (1-2 mg/kg IM)
**Morphine**: Dog (0.1-0.2 mg/kg IM); Horse (0.1 mg/kg IM)
**Xylazine**: Dog (0.5-1.0 mg/kg IM); Horse & Cattle (0.05-0.2 mg/kg IV)

**For objectlves e and f**:
**Atropine**: Dog & Cat (0.04-0.06 mg/kg IM / IV);Sheep & Goat (0.2 mg/kg IV); Horse (0.01 mg/kg IM)
**Glycopyrrolate**: Dog & Cat (0.01-0.02 mg/kg IM)

**For objective g**:
**Diazepam**: Species and doses as given above
**Gallamine**: All species (0.25-0.5 mg/kg IM)
**d-Tubocuraine**: All species (0.20-0.60 mg/kg IV)
**Xylazine**: Dog (0.5-1.0 mg/kg IM); Horse & Cattle (0.05-0.20 mg/kg IV)

**For objective h**:
**Acepromazine**: Species and doses as given above
**Chlorpromazine**: Species and doses as given above
**For objective i**: To empty the GIT: **Purgatives;** to sterilize the GIT **broad spectrum antibiotics**

## Chapter – 17: SEDATIVES, HYPNOTICS AND ANTICONVULSANTS

**Sedatives** are drugs which reduce CNS excitation without inducing sleep. Under sedation the animals remain awake, but are calm and free from nervousness.

**Hypnotics** are drugs that cause hypnosis, a condition characterized by CNS depression resembling normal (arousable) sleep. Hypnosis is derived from 'Hypnos', the Greek god of sleep.

Both sedatives and hypnotics do not possess analgesic property, but dull the perception of pain sensation. Hypnotics in higher doses cause deep sleep (narcosis) and hence are also called as narcotics. Hypnotics include:

**Barbiturates**: These are commonly used as sedatives/hypnotics in dog and cat:

| Barbiturate | Oral Dosage (mg/kg/day) * | |
|---|---|---|
| | Dog | Cat |
| Barbitone | 150 – 1000 | 100 – 250 |
| Phenobarbitone | 30 – 300 | 15 – 60 |
| Amobarbitone | 5 – 10 | |
| Secobarbitone | 30 – 200 | |

* Depending upon the duration of effect desired, repeat at 8 – 12 hr intervals in a day.

**Benzodiazepines**: Classified based on their pharmacotherapeutic use:

a) Hypnotics: Diazepam, flurazepam, nitrazepam and flunitrazepam
b) Anxinolytics: Diazepam, chlodiazepoxide, oxazepam and lorazepam
c) Anticonvulsants: Diazepam and clonazepam

Benzodiazepenes are commonly used as sedatives or hypnotics in man and dog. All the drugs have high therapeutic index, hypnotic doses do not affect respiration or CV functions or other systems. These also do not induce microsomal enzymes. Their toxicity (due to higher dosage) can be overcome by giving specific benzodiazepine receptor antagonist **flumazenil**.

**Mechanism of Action**: Benzodiazepenes preferentially act on mid brain ascending reticular formation (maintains sleep-wakefulness cycle) and on limbic system (thought and mental functions). Their mechanism of action is through enhancing presynaptic or postsynaptic inhibition of specific benzodiazepine receptor which is an integral part of $GABA_A$ receptor-$Cl^-$ channel complex. These exert only GABA facilitation, but not GABA mimetic action (no selective increase in $Cl^-$ conductance). GABA modultes activation of $Cl^-$ channels within the neuronal membrane of excitable neurons.

**Pharmacokinetics**: Oral absorption of benzodiazepines differs due to their variation in lipid solubility. These drugs due to lipid solubility gain access into CNS. Benzodiazepines are metabolized in liver through dealkylation and hydroxylation and the metabolites (glucuronide conjugates) are excreted through urine. Most of the benzodiazepine drugs have active metabolites (chlordiazepoxide, desmethyldiazepam, diazepam, flurazepam etc) which undergo enterohepatic recycling (have long half-lives). Chlorazepine is metabolically activated to desmethyldiazepine, which is further metabolically activated to oxazepam.

**For doses of diazepam see under Tranquilizers (below).**

**Zolpidem** though not a benzodiazepine derivative acts like them on central benzodiazepine receptor on chloride channel and potentiates GABA action.

**Chloral Hydrate**: It is used as hypnotic/sedative in large animals either orally or IV. Cattle, Horse and Swine: 5-7 gm/100kg or 2.5-3.5 gm/50 kg orally in 500-1000 ml lukewarm water or 20-30 gm/animal IV.

**Paraldehyde**: It is a condensation product of three molecules of acetaldehyde. It is a volatile liquid with irritant and inflammable properties. Paraldehyde is a potent short acting hypnotic, with no anticonvulsant or analgesic action. It is especially useful in controlling emergency convulsions (like tetanus and status epilepticus), however better drug is diazepam. It is metabolized through conversion to acetaldehyde and then to $CO_2$ and $H_2O$.

The general **therapeutic uses of sedatives and hypnotics** are:
a) As chemical restraints (to restrain or quieten an excited animal for clinical exam).
b) To induce sleep and c) As preanaesthetics.

**Anticonvulsants**

These drugs are used to counteract nervous disorders characterized by convulsions or epilepsy (antiepileptics) or in convulsive diseases or poisonings. The major anticonvulsant drugs are:

**Phenobarbitone**: Inhibition of motor and sensory cerebral cortex. Acts by enhancement of GABA activity and inhibition of glutamate mediated excitation.
Dog: 2-10 mg/kg/day orally twice a day; Cat 1-2 mg/kg orally twice a day; Horse: 2.5-10 mg/kg orally once a day.

**Phenytoin**: Inhibition of motor area of cerebral cortex. It also stabilizes the nerve junctions by interfering with sodium ion permeability (blocks sodium ion channels).
Dog: 6-30 mg/kg orally thrice a day; Horse: 3-15 mg/kg orally thrice a day (8 hr intervals).
Phenytoin increases metabolism of digitoxin, DDT, cortisol and dexamethasone. Chloarmphenicol and phenylbutazone decrease its metabolic breakdown and elevate its plasma levels. Phenytoin prolongs prothrombin time, which is reversed by vitamin K.

**Primidone**: Prodrug, converted to active metabolite phenobarbitone (in liver).
Dog: 10-30 mg/kg orally in divided doses at 8 hr intervals.
Chloramphenicol potentiates its CNS depressant effect by inhibiting microsomal enzymes.

**Diazepam**: Most commonly used benzodiazepine. Acts by enhancing central inhibitory transmission processes mediated by GABA. (See sedatives and tranquilizers). Also used as preanaesthetic sedative. It is not administered orally (poor aborption, elimination and development of tolerance). It is the drug of choice in status epilepticus in dog.
Dog: 0.5-1.5 mg/kg IV, repeat within 30 min to 2 hr if needed; 0.5-2 mg/kg, tnrice a day; per rectum); Cat: 0.5-2 mg/kg IV; Horse: 20-40 mg/kg IV.

**Clonazepam**: A benzodiazepine used orally in dog: 0.5 mg/kg orally, twice or thrice a day.

**Carbamazepine**: Acts by decreasing the excitability on neuronal membrane through interfering with $Na^+$ conductance.

**Bromides** (Sodium/Potassium salt): Dog and Horse: 15-30 mg/kg orally in two divided doses in a day.

**Valproic acid**: Acts through inactivation of sodium channels like phenytoin and by increasing synthesis and decreasing degradation of GABA. Dog: 10-50 mg/kg orally thrice a day.

**Lamotrigine**: Acts through blockade of presynaptic $Na^+$ channels, reducing the release of excitatory transmitter glutamic acid in glutaminergic nerves.

**Gabapentin**: Interfers with the action of central excitatory transmitter glutamic acid by preventing its release from glutaminergic nerve terminals.

**Vigabatrin**: Acts through increasing the concentration of central inhibitory transmitter GABA by inhibiting GABA transaminase, which inactivates GABA.

**Tiagabine**: Acts by prolonging the action of central inhibitory transmitter by inhibiting its neuronal re uptake.

**Propofol**: Also a GABA agonist Dog & Cat: 1-2 mg/kg IV.

Newrer Drugs: Vigabatin (inhibition of GABA transaminase), Felbamate, gabapentin, topiramate, zonisamide (related to sulfonamides).

## Chapter – 18: TRANQUILIZERS AND ANTIPSYCHOTICS

Tranquilizers are the drugs that produce tranquility or calm down an excited animal. Also called ataractics (ataraxia: undisturbed state). Tranquilizers, neuroleptics or antipsychotic drugs are similar (human medicine). The therapeutic uses of tranquilizers include:

a) As preanaesthetic sedatives for smooth induction of anaesthesia and reduce the dose of anaesthetic.
b) To calm down or quieten an excited animal for clinical exam (chemical restraint).
c) To relieve the stress of transport or vomition (motion sickness).

**Classification**: Derivatives of a) Phenothiazine b) Thioxanthine c) Benzodiazepines d) Butyrophenone e) Rauwolfia derivatives

**Phenothizine Derivatives**: Chlorpromazine, Promazine, Triflupromazine and Acepromazine.

These drugs cause sedation and reduce spontaneous motor activity through antagonism of central neurotransmission of dopamine by preventing its interaction with the excitatory receptors (block $D_1$ (++) and $D_2$ (+++) receptors). Their antiemetic effect is through blockade of dopamine receptors in CTZ. They also antagonize central stimulant action of sympathomimetics, but not the convulsions caused by strychnine or picrotoxin (CNS stimulants) and morphine excitation in cats. They cause hypothermia through depletion of catecholamines in hypothalamus. Phenothiazine tranquilizers block conditioned avoidance response (CAR), but not the unconditioned avoidance response (blocked by sedatives). They also block α-adrenergic, $H_1$ and $5HT_2$ receptors in CNS. In addition to above the tranquilizers also exert the following pharmacological actions:

Peripheral autonomic effects include α-adrenergic receptor blockade, hyperglycaemia, anticholinergic, antihistaminic, antispasmodic and antiarrhythmic effects (quinidine-like depressant effect on myocardium); curariform effect and inhibition of intestinal secretions.

Phenothiazine tranquilizers should not used for control of epileptic seizures (lower seizure threshold).

**Doses and Route of Administration of Phenothiazine Tranquilizers**:

**Chlorpromazine**: Dog: Sedative or tranquilizer 0.5-4 mg/kg IV or 1-5 mg/kg IM; Cat: 1-2 mg/kg IV, IM or SC; Pig: 0.5-4.5 mg/kg IM Cattle as preanaesthetic @ 0.2 mgkg IM

**Promazine**: Dog: As antiemetic 1-2 IM mg/kg; preanaesthetic, sedative or tranquilizer 2-5 mg/kg IM or IV; Cat: As sedative or tranquilizer: 2-4 mg/kg IM or IV; Horse: As sedative or tranquilizer 0.5-1 mg/kg IM or IV; Cattle: As sedative in nonlactating 0.5-1 mg/kg IM or IV; Swine: As sedative, tranquilizer or preanaesthetic 0.5-1 mg/kg IM or IV.

**Acepromazine**: Dog: As preanaesthetic: 0.05-0.1 mg/kg IM or IV; Cat: Tranquilizer: 0.1-0.2 mg/kg SC, IM or IV; Preanaesthetic 0.1 mg/kg IM; Sedative 1-2 mg/kg orally; Horse: As sedative in colic: 0.05-0.01 mg/kg SC, IM or IV; as preanaesthetic 0.02-0.04 mg/kg IV; Cattle: As sedative or tranquilizer: 0.05-1 mg/kg SC, IM or IV; Swine: Sedative, tranquilizer or preanaesthetic: 0.1-0.2 mg/kg SC, IM or IV.

**Triflupromazine**: Dog: As tranquilizer 1-2 mg/kg IV or 2-4 mg/kg IM; as preanaesthetic 2-4 mg/kg IM; Cat: As preanaesthetic 4-8 mg/kg IM; Horse: As tranquilizer 0.2-0.3 mg/kg IM or IV.

Administration of the above drugs as sedatives or tranquilizers needs to be repeated at 4-8 hr intervals in a day as per the response of the animals. As preanaesthetics they need to be administered 30 min to 1 hr before anaesthesia.

**Thioxanthine Derivatives**:

Pharmacological effects similar to phenothiazine derivatives (blockade of $D_1$ (+) and $D_2$ (+++) receptors in CNS:

**Chloprothixene**: Has antiemetic and antihistaminic effects. Its sedative and tranquilizer doses are: Dog: 2-4 mg/kg IM or IV; Small livestock: 0.5 mg/kg IV.

**Butyrophenone Derivatives**: These block motor activity, suppress the adverse effects of stress and trauma and have antiemetic effect. Their action is through antagonism of dopamine antagonism through blockade of $D_1$ (+) and $D_2$ (+++) receptors in CNS. These drugs also exert peripheral adrenergic blockade.
**Droperidol**: Most potent antiemetic. It is used in combination with fentanyl as neuroleptanalgesic.
**Haloperidol**: Used as tranquilizer and as antiemetic in dog (0.05-0.1 mg/kg IM or IV).
**Azaperone**: Used as tranquilizer in pigs (2 mg/kg IM) and horses (0.5-0.75 mg/kg IM)
**Note**: Administration of catecholamines is contraindicated in animals pretreated with phenothiazine or butyrophenone tranquilizers (results in severe hypotension due to alpha adrenergic receptor blockade).
**Benzodiazepine Derivatives**: These drugs exert central depression ranging from sedation through hypnosis to anticonvulsant effect and relaxation of skeletal muscles. Their mechanism of CNS depressant effect is through enhancement of the action of GABA by specifically binding to a regulatory site (benzodiazepine receptor) on the $GABA_A$ receptor, thereby increasing the affinity of the GABA to its receptor and facilitating the opening of GABA-activated chloride channels. These drugs have no significant effect on cardiovascular and respiratory system at sedative or tranquilizer doses. The most commonly drug under this group is
**Diazepam**: Dogs: As sedative: 1 mg/kg orally or IV; Anticonvulsant: 1-2 mg/kg IV; preanaesthetic: 0.2-0.5 mg/kg IM or IV; Calves: As sedative: 0.4 mg/kg IV; Cat: 1 mg/kg IV; Horse: 0.05-0.5 mg/kg IV; Cattle: 0.5-1 mg/kg IV; Pig: 1-10 mg/kg IM.
Other benzodiazepines used in man include: Lorazepam, oxazepam, temazepam, nitrazepam, chlodiazepoxide, flurazepam, chlonazepam, midazolam, zolpidem etc.
**Rauwolfia Derivatives**: Reserpine is the alkaloid obtained from the roots of an Indian medicinal plant *Rauwolfia serpentina*. It is used as a tranquilizer and as an antihypertensive drug in man. In vety practice other tranquilizers are preferred to reserpine. Metoserpate HCl a synthetic analog of reserpine is used as tranquilizer for flock treatment of birds before handling @ 568.5 mg/3.8 litres of drinking water or at 150 ppm level in feed.

**Antipsychotics**
These drugs are used in psychological disorders or affective disorders. Affective disorders are nervous disorders characterized by abnormal mood. The abnormal mood changes are: 1) **Depression** and 2) **Mania.** Therefore these drugs are of two types: 1. **Antidepressants** and 2. **Antimaniac drugs**.
**Antidepressants:**
Are drugs used in the treatment of abnormal mood and behaviour due to depression. These drugs are also called as Thymoleptics or Mood Elevators.Depression is characterized by feeling of sadness or misery, loss of concentration or self confidence, disinterest in surroundings, loss of libido, anorexia, lowered energy and insomnia (sleeplessness) or hypersomnia (excessive sleep). Pharmacologically it is due to deficiency of monoamines in limbic system in brain. Depression is treated by administering antidepressants.

**Classification and Mechanisms of Action of Antidepressants:**

| Types | Examples | Mode of Action |
|---|---|---|
| Tricyclic Anti-depressants | Imipramine, Desipramine, Amitriptyline, Protriptyline, Clomipramine, Doxepin, Amoxapine, Mitrazapine, Nifazadone, Trazodone, Maprotilne | Act by inhibiting uptake of noradrenaline and/or 5-HT by monoaminergic nerve terminals, thus acutely facilitating transmission. Potent $H_1$ blockers. Inhibit one or both forms of brain MAO: Increase stores of noradrenaline, dopamine and 5-HT in nerve terminals. Inhibition of both MAO types correlates with antidepressant activity. |
| Monoamine Oxidase (MAO) Inhibitors | Phenelzine, Tranylcypromine Isocarboxazid, Moclobemide Iproniazid, Selegiline | |
| 5-HT re uptake Inhibitors | Fluoxetine, Fluvoxamine, Paroxetine, Sertraline, Citralopram, Reboxitine, Paroxetine | Act by inhibiting uptake of 5-HT by tryptaminergic nerve terminals, thus acutely facilitating 5-HT transmission. |

$MAO_A$ enzyme is specific to epinephrine and norepinephrine and $MAO_B$ is specific to dopamine and 5-HT. Cheese, wine and chocolate contain tyramine, which degraded in liver by $MAO_A$ before systemic absorption. Ingestion of these foods in patients under MAO inhibitor antidepressant therapy results in severe hypertensive crisis (Tyramine is absorbed and taken up by the adrenergic nerves, converted to octopamine, a false transmitter, which releases norepinephrine from adrenergic nerve terminals).

**Hypericin** (from *Hypericum perforatum*, Saint John's Wort) is an inhibitor of MAO; exerts antidepressant effect and it also has germicidal and anti-inflammatory effects.

**Methylphenidate** acts as an antidepressant by increasing dopamine levels promoting norepinephrine formation, especially in cerebral cortex causing mood elevation.
Maprotiline and amoxapine block re uptake of norepinephrine. Mitrazapine, nifazadone and trazodone increase central serotonergic nerve outflow/activity and by inhibiting serotonin re uptake.

Clomipramine or Amitriptyline: Dog: 1-3 mg/kg orally twice a day; Cat: 0.5-1 mg/kg orally once a day.
Doxepin: 0.5-2 mg/kg orally twice a day.
Fluoxetine: Dog & Cat: 0.5-1 mg/kg orally once a day.

**Antimaniac Drugs:**
**Mania** is characterized by excessive exuberance, enthusiasm, over self confidence, impatient, easy irritability, aggressive bahaviour or hyperactivity and improper judgement. Pharmacologically it is due to dopaminergic overactivity in the limbic system in brain.

Drugs for treatment of mania are: 1) Lithium carbonate, 2) Carbamazepine and 3) Valproate. These drugs are also called as mood stabilizing drugs.
Lithium is a small monovalent cation ($Li^+$). Lithium readily enters excitable cells through the Na channels displacing intracellular K+. The influx of K+ is reduced by inhibition of Na+/K+ ATPase and the electrical gradient of K+ (increased extracellular K+ level). The reversal of K+ levels results in lowered neuronal excitability causing calming of the maniac individual. It also reduces release of norepinephrine and dopamine in brain, without affecting 5-HT release. Lithium is also believed interfere with the transduction mechanisms of central adrenergic receptor activation through decreasing the formation of second messengers cAMP and $IP_3$. Thus, lithium is acting through decreasing neuronal excitability and correcting the imbalance of turnover and/or actions of monoamines in brain.

Valoproic acid, carbamazepine and gabapentin are also used as antimaniac drugs.
Valproic acid: Dog; 10-50 mg/kg oraliy thrice a day.
Carbamazepine: Cat: 25 mg orally twice a day.
Lithium carbonate: Dog; 75 mg orally twice a day

# Chapter – 19 ANALGESICS

## 1. Introduction

Algesia = Pain; Algesic = Pain inducer; Hyperalgesia = Enhanced pain sensation
Analgesia = Loss of pain sensation
Analagesics are drugs that cause analgesia i.e. drugs used for relief of pain.

**Classification:** Mainly Two Groups:
A. **Narcotic Analgesics**: Cause analgesia accompanied by narcosis (deep sleep): **Opioid Analgesics**
a) Opium Alkaloids b) Morphine derivatives c) Morphine substitutes
B. **Nonnarcotic Analgesics (NSAIDs)**: See later (below)

| **Differences between** | **Narcotic and** | **Nonnarcotic Analgesics** |
|---|---|---|
| 1. CNS depression: | Narcosis (sedation-hypnosis) | No significant depression |
| 2. Type of analgesia: | Deep-seated (visceral) intense pain | Superficial pain (skin/joints/ muscles) |
| | Potent analgesia (+++++) | Less potent analgesia (++) |
| 3. Antipyretic effect: | Absent | Potent |
| 4. Antiinflammatory effect: | Absent | Potent |
| 5. Antirheumatic, antiarthritic and uricosuric or antigout effects: | Absent | Present |
| 6. Toxicity: | High | Low |
| 7. Addiction: | Potently addictive | Absent |

**Ideal Analgesic**: Should produce satisfactory analgesia with rapid on set and of long duration, and should not have adverse effects or side effects on other systems of the body. Should not pose a problem of addiction or physiological dependence and should be least toxic.

## 2. Narcotic Analgesics

**Opium**: It is the dried crude exudate obtained from the unripe seed capsules of the poppy plant *Papaver somniferum*. The pharmacologically active principles of opium are alkaloids. Opium contains 32 alkaloids, divided into two groups (important examples are given below):
1. Phenanthrene group : Morphine, Codeine and Thebaine
2. Benzylisoquinoline group : Papaverine, Noscapine and Narceine

| **Differences between** | **Phenanthrene Group and** | **Benzylisoquinolene Group** |
|---|---|---|
| 1. CNS Effect: | Depression or Excitation | No significant effect |
| 2. Analgesia: | Significant, except thebaine | Insignificant |
| 3. Effect on smooth muscles: | Spasmogenic | Spasmolytic |
| 4. Addiction: | Common | Uncommon |

**Morphine**: The principal alkaloid of opium and the first plant alkaloid isolated (by Friedrich W.A. Serturner, a German apothecary (Hanover) in 18[illegible]; named so after the Greek God of dreams Morpheus).

**Major Pharmacological Effects of Morphine** (opioid prototype):

a) **On CNS**: Depression or Excitement depending on species. Euphoria (feeling of well being, opposite to dysphoria). Depression in man, monkey and dog. Excitement in cat, cattle, sheep, goat and horse. Morphine produces convulsions in a spinal dog (only spinal cord intact: stimulatory effect on spinal cord; hence not used to counteract strychinine convulsions). Has analgesic effect due to central (supraspinal) and peripheral actions, blocks the nocieption transmission i.e. antinociception). Relieves acute or chronic deep seated pain (due to tissue injury, inflammation or tumour growth) without impairing motor activity.

b) **On GIT**: The ultimate effect is severe constipation. First morphine causes emptying of GIT through vomition and defaecation. Then it causes persistent and intense spasmogenic effect on smooth muscles of intestines (cholinergic and histaminergic effects) and constriction of sphincters interfering with peristalsis causing delayed passage of ingesta, increased absorption of water and dryness of ingesta. Morphine also suppresses the defaecation reflex and causes constriction of anal sphincter causing severe constipation.

c) **On Respiration**: Depression, accompanied by reduced sensitivity of respiratory centre to $PCO_2$, but at higher doses causes direct depression of medullary respiratory centre. Bronchoconstriction due to histamine release by morphine.

d) **On CV system**: No significant effect at analgesic doses. No effect on medullary vasomotor centre. Hypotension due to histamine release. At higher doses causes fall in BP and bradycardia due to depression of vasomotor centre.

e) **On Cough Centre**: Potent antitussive (cough suppressant) by depression of cough centre.

f) **On Emetic Centre**: Nausea and vomition through stimulation of CTZ at analgesic doses. Morphine causes simulated vomition following local application to the floor of IV ventricle in dogs from which GIT is removed, showing central emetic action, but not due to effect on GIT.

g) **On Pupil (Eye)**: Marked dilatation in horse, monkey, sheep, cattle etc, but pin point constriction in man (diagnostic), dog, rat and rabbit. Bird's pupil size is not altered due to presence of nonresponsive skeletal muscle (sphincter muscle of iris).

h) **Body Temperature**: Hypothermia in man, monkey, dog and rabbits, but in other animals hyperthermia. Hypothermia is due to release of 5-HT in hypothalamus which is reversed by TRH, considered as physiological antagonist of morphine.

i) **On Kidney**: In dog morphine initially causes urination and later oliguria or anuria due to release of ADH, increase in tone of urinary bladder and constriction of bladder sphincter.

j) **Neuroendocrine Action**: Morphine interferes with hypothalamic activity and decreases the release of FSH, LH and ACTH and increases the release of prolactin and GH.

The pharmacological effects of morphine (other opioids and opioid like drugs) are through interaction with opioid receptors μ (mu), κ (Kappa), δ (delta) and σ (sigma) and which are present in neurons. The mu, kappa and sigma receptors are named so after morphine, ketocyclazocine and SKF 10147 respectively. Morphine euphoria is μ effect, and dysphoria of other opioids is κ effect. The mu receptors are associated with most of the analgesic effects of opioids and some undesirable effects such as respiratory depression, narcosis and drug dependence. The delta receptors contribute to analgesia and some peripheral effects like reduced GI motility and miosis etc. The K receptors contribute to spinal analgesia, sedation and dysphoria. The sigma receptors are not true opioid receptors (not activated by morphine), but are activated by other oipoids like pentazocine and butorphanol and nonopioids phencyclidine producing psychomimetic action (hallucinations) and dysphoria (sometimes by opioids).

**Opioid Receptor Agonists and Antagonists**

**Agonists:** **Stong:** Fentanyl. heroin, meperidin, methadone, morphine and sufentanil.
**Moderate**: Codeine and propoxyphene

**Partial Agonist:** Buprenorphine (μ receptors)

**Mixed Agonists-Antagonists**: Pentazocine (agonist to K and σ; weak antagonist to μ and σ receptors.
**Antagonists**: Naloxone, naltrexone and nalmefene (derivative of naltrexone, considered a pure antagonist, used in opioid overdosage)
**Physiological Nociceptive Pathway**: Nociception is painful sensation due to noxious stimulus which may be due to mechanical, thermal or chemical injury to the tissues. Physiologically when there is a noxious stimulus the sensory nerve endings are activated triggering release of chemical mediators of pain and inflammation such as Substance P (SP), bradykinin, 5-HT, histamine, calcitonin gene-related peptide (CGRP), nerve growth factor (NGF), neurokinins (NKA and NKB), ATP, prostaglandins and anandamine, some of which cause intense pain and the others help in propagation and/or excitation of the neurons in the nociception pathway through the dorsal horn of spinal cord and the supraspinal sites like thalamus, hypothalamus and ultimately to the sensory cortex, where the pain sensation is finally felt. However, the body fights against the pain, the intensity of nociception is gradually lowered, thereby pain subsides through the interplay of physiological pain relievers, the endogenous mediators (which mimic the effects of morphine) released by the neurons. These are chemically identified and therefore collectively called as opioid peptides which include leucine enkephalin, methionine enkephalin, dynorphin and β-endorphin in peripheral and CNS neurons. The components of nociception pathway peraqueductal grey, nucleus raphe magnus and substantia gelatinosa are rich in opioid neurons.

**Mechanism of Analgesic Effect of Opioids**: The analgesic effect of opioid analgesics is through their action on opioid receptors. These are G-protein coupled receptors and the action is involved through inhibition of adenylate cyclase causing decrease in intracellular second messenger cAMP. They are also linked to ion channels (G-protein coupled ion channels), interaction with which results in opening of K channels and inhibition of opening of $Ca^{++}$ channels causing hyperpolarization and nonrelease of pain inducers (see above). Thus the opioid analgesics block nociception neuronal pathway. Hence the pain sensation is not felt.

**Morphine Metabolism**: It is metabolized through conjugation in liver to form glucuronides morphine-3-glucuronide and morphine-6-glucuronide. The later has more analgesic effect than morphine and the former is morphine antagonist. The conjugates are excreted through bile in intestines (glucuronides are hydrolyzed in intestines and morphine is reabsorbed through enterohepatic recycling).

**Therapeutic uses of Morphine**: Generally used in dogs:
a) As analgesic (0.25-0.75 mg/kg sc; 4-6 times a day)
b) As preanaesthetic (0.1-2 mg/kg sc)
c) As postanaesthetic to relieve post operative pain and prevent injury (dose as in (a).
d) For control of severe diarrhoea (0.05 mg/kg orally).
Analgesic Doses of Morphine in other species:
Cat: 0.1 mg/kg IM or SC; Horse (acute colic): 0.2-0.5 mg/kg IM; Pig: 0.25-1 mg/kg IM 6 times a day.

**Contraindications of morphine in dogs**: Uraemic conditions
a) Tetanus, epilepsy and strychnine poisoning
c) Traumatic/haemorrhagic shock

**Morphine Toxicity**: Opium toxicity results due to grazing on stems or capsules of opium. The toxic signs are CNS excitation and constipation. Long term use of morphine in dogs causes addiction/physiological dependence, when sudden withdrawal results in appearance of abstinence syndrome characterized by hyper irritability, excessive motor activity (body shakes, writhing, jumping and signs of aggression), teeth chattering and weight loss. Addiction is common in man (in addition to above, also show frequent yawning, dilated pupil, fever, sweating, piloerection, nausea, diarrhoea and insomnia. The subject is extremely restless and distressed and has strong craving for the drug).

**Morphine Derivatives** (Morphine analogues):
These are semisynthetic derivatives of morphine and are closely related in chemical structure to morphine:

a) **Methyl morphine** (Codeine): Though less potent than morphine, selectively depresses medullary cough centre. Codeine phosphate is used as an oral anticough drug (antitussive). Metabolized to morphine. Oral Doses: Dog: 15-60 mg; Horse & Cattle: 0.2-2.0 Gm.
b) **Dimethylmorphine** (Thebaine): Weak analgesic.
c) **Diacetylmorphine** (Heroin): Causes strong addiction, hence no therapeutic application.
d) **Hydromorphone**: More potent analgesic than morphine. Dog: 1-2 mg/kg sc
e) **Oxymorphone**: More potent analgesic than hydromorphine. Dog & Cat: 0.1-0.2 mg/kg sc, IM or IV once in a day; Horse: 0.025 mg/kg IM or IV; Pig: 0.2 mg/kg IM.
f) **Dihydromorphine**: More potent analgesic than morphine
g) **Apomorphine**: A morphine derivative with potent central emetic action.

**Morphine Substitutes**:
Synthetic oipoid like analgesics unrelated in chemical structure to morphine:

a) **Pethidine or Meperidine**: Similar to morphine, except that it causes restlessness than sedation. Also has antimuscarnic effect: relaxes smooth muscles of intestines (intestinal spasmolytic). Doses: Dog & Cat: 2.5-10 mg/kg IM or SC every 2-3 hr; Horse: 0.2-0.5 mg/kg IV;; Cattle: 500 mg IV; Pig: 5-10 mg/kg IM or IV. **Difenoxin**, structurally similar to meperidine, can also be used as an antidiarrhoeal. Diphenoxylate a meperidine-like opiate with minimal euphoric or addictive properties.
b) **Methadone**: Similar to morphine, but its duration of action is longer than morphine.
c) **Fentanyl** and Sufentanil: More potent, but shorter in duration of action than morphine
d) **Pentazocine**: Mixed agonist (delta and kappa) and antagonist (mu). Effects similar to morphine, but at high doses causes dysphoria rather than euphoria as seen with morphine. Dog & Cat: 2-3 mg/kg IM; Horse: 0.25-0.3 mg/kg IV; Pig: 2-5 mg/kg IM at 4 hr intervals.
e) **Butorphanol**: More potent than morphine or pentazocine. Dog & Cat: 0.2-0.4 mg/kg IM or SC at 4-6 hr intervals; Horse: 0.05-0.1 mg/kg IM or SC: Pig: 0.1-0.25 mg/kg IM.
f) **Nalbuphine**: Dog: 0.5-2 mg/kg SC every 6-8 hr intervals; Cat: 1-2.5 mg/kg IV every 3-4 hr intervals.
g) **Loperamide**: Opiate antidiarrhoeal used in inflammatory bowel disease.

**Dose of fentanyl + droperidol** (1 ml contains 20 mg droperidol and 0.4 mg fentanyl):
As neuroleptanalgesic in a dog of 5-10 kg body weight 1 ml IM or for a dog of 10-20 kg body weight 1 ml IV.
As general anaesthetic in dog: 1 ml per 18 kg IM 10 min after administration of penobarbitone @ 6.6 mg/kg IV or 1 ml per 10-25 kg IM immediately after administration of pentobarbitone @ 6.6 mg/kg IV.
Droperidol-fentanyl combination is not used in ruminants (due to excessive CNS stimulation).
**Thebaine Derivatives**: Synthesized from thebaine: **Etorphine** and **Buprenorphine**: These drugs cause neuroleptanalgesia (analgesia + neurolepsia i.e .tranquility). Etorphine is 1000 times more potent than morphine and is used to immobilize wild animals for trapping: 1-2 mg/kg IM (dose for an elephant can be accommodated in a dart). Buprenorphine is a partial agonist on mu receptors.
Buprenorphine: Dog: 0.01-0.02 mg/kg SC twce day; Cat: 0.01 mg/kg SC or IM twice a day; Pig: 0.01-0.02 mg/kg IM 2-4 times in a day.
**Morphine Antagonists (Narcotic Antagonists)**:
Naloxone, diprenorphine, naltrexone and nalmefene (a derivative of naltrexone): Competitive antagonists of mu (+++), delta (+) and kappa (++ / +++) receptors. Nalmefene is considered as a pure antagonist and hence preferred in opioid overdosage.
Nalorphine, also a morphine derivative is a mixed or partial agonist (kappa) and antagonist of morphine (mu). Apomorphine, another derivative of morphine is a potent central emetic.

## 3. Nonnarcotic Analgesics: NSAIDs

These drugs are popularly called as nonsteroidal antiinflammatory drugs: NSAIDS. They exert varying degrees of antipyretic, analgesic and antiinflammatory effects. The NSAIDs are classified as below:

**Based on Chemical Grouping:**
A) Salicylates: Sodium salicylate and acetyl salicylic acid (aspirin)
B) Paraaminophenol Derivatives: Paraacetanol (acetaminophen), phenacetin, aminopyrin and antipyrin
C) Pyrazolon Derivatives: Phenylbutazone and oxyphenbutazone
D) Indoles and Related Drugs: Indomethacin and sulindac
E) Phenylacetic Acid Derivaritices: Diclofenac, tolmetin and ketorolac
F) Propionic Acid Derivatives: Ibuprofen, naproxen, fenoprofen, ketoprofen and flurbiprofen
G) Fenamates: Mefenamic acid
H) Oxicams: Piroxicam, tenoxicam, lornoxicam and meloxicam
I) Sulphonanilide Derivatives: Nimesulide

**Based on Selectivity of COX Inhibition:** cyclo-oxygenase-1 (COX-1)
A) Nonselective COX inhibitors (Selective COX-1 and slight COX-2 inhibition): Salicylates, propionic acid derivatives, phenylacetic acid derivatives, paraaminophenol derivatives, and pyrazolon derivatives.
B) Slight to moderate selective COX-2 inhibitors (< 5 to 50 fold COX-2 inhibition): Oxicams, indomethacin, nimesulide, etodolac and celecoxib. These drugs also cause complete or significant COX-1 inhibition.
C) Highly selective COX-2 inhibitors (> 50 fold COX-2 inhibition): Rofecoxib and deracoxib. Also possess some COX-1 inhibition also

**Antipyretic Effect**: Normal body temperature is maintained by thermoregulatory centre (thermostat) in hypothalamus, which ensures a balance between heat production and heat loss. Fever occurs due to disturbance in the hypothalamic thermostat, which is set at a high temperature. The antipyretics act by resetting the thermostat to normal set-point and then the body temperature regulating mechanisms (dilatation of superficial blood vessels, sweating and increased respiration, promoting heat loss) operate to lower the elevated body temperature to normal level. Normal body temperature is not affected by NSAIDS or antipyretics (at therapeutic doses).
During infections and inflammatory reactions the pathogenic microbial endotoxins cause release of pyrogen interlukin-I from macrophages, which stimulates the generation of prostaglandins (E series) in hypothalamus, which set the thermostat at a higher level resulting in pyrexia or fever. The NSAIDs exert antipyretic effect by irreversibly inhibiting the enzyme cyclo-oxygenase 1 (COX-1) or cyclo-oxygenase 2 (COX-2) or both which catalyze the initial reaction of prostaglandin formation from arachidonic acid in the hypothalamus or through inhibition of a specific COX isoenzyme in the CNS.
COX-1 is a constitutive enzyme, responsible for physiological synthesis of prostaglandins for tissue homeostasis (including protection on gastric mucosa; $PGI_2$ and $PGE_2$). Whereas, COX-2 is an inducible enzyme responsible for synthesis of protanglandins whch have a role in fever, pain and inflammation.

**Analgesic Effect**: The NSAIDS are mainly effective against pain associated with arthritis, bursitis, muscular pain, vascular pain, toothache, dysmenorrhoea and bone pain, in all the conditions there is increased synthesis of pain inducers and prostaglandins. The prostaglandins sensitize nociceptors to pain inducers (SP, 5-HT, histamine, CGRP, NGF, NKA and NKB). The NSAIDS exert analgesic effect by inhibiting prostaglandin synthesis through irreversible inactivation of COX-1 or COX-2 or both.

**Antiinflammatory Effect**: The inflammatory reactions such as vasodilatation, increased vascular permeability, cell proliferation, pain etc are mediated by the release of a multitude of chemical mediators having varied mechanisms of action. The inflammatory stimuli in the inflammatory cells induce synthesis of prostaglandins through COX-2. The NSAIDS exert antiinflammatory effect by inhibition of prostaglandin synthesis by irreversible inhibition of this enzyme (Also see Autacoids).
Aspirin in addition to above three effects also prolongs clotting time by preventing platelet aggregation (treatment of coronary blocks, myocardial infarction and angina). This effect is due to irreversible inhibition of $TXA_2$ synthesis in platelets. Continued use of aspirin, especially on empty stomach, leads to gastric bleeding and uiceration (due to inhibition of $PGI_2$ and $PGE_2$ production inhibition of constitutive COX-1 also). To minimize the adverse effects of NASAIDs, selective COX-2 inhibitors are being evaluated.

**Relative Potency of NSAIDS** (Non-steroidal Anti-inflammatory drugs)

Antipyretic Effect : Aspirin = Paracetamol > Phenacetin > Phenylbutazone
Analgesic Effect : Aspirin > Phenacetin and Paracetamol > Phenylbutazone
Antiinflammatory Effect : Phenylbutazone > Aspirin

Sodium salicylate is less potent than aspirin as antipyretic, analgesic and antiinflammatory.

**Phenylbutazone** is a prodrug, its effects are due to metabolic conversion to oxyphenbutazone. It is commonly used in treatment of lameness due to muscle or joint pains in horses (doping agent). It also has uricosuric/antigout effect (increase in excretion of uric acid by preventing its absorption in renal tubules). Due to its high protein binding affinity it displaces other drugs bound to the plasma proteins and thus increases their effects (warfarin haemorrhages). Phenylbutazone increases sodium and water retention by a direct action on renal tubules causing increased plasma volume and oedema (not to be used in CHF).

**Indomethacin**: Potent antiinflammatory and uricosuric agent as phenylbutazone.

Dipyrone in addition to above AAA effects, also has spasmolytic effect on intestinal smooth muscles.

[**Other Anti-Gout Drugs**: Allopurinol (inhibits xanthine oxidase which catalyzes formation of uric acid from xanthines; xanthines are diverted for purine/nucleic acid synthesis), Probenecid (reduces uric acid reabsorption in renal tubules and thus promotes its urinary excretion), sulfinpyrazone, acetaminophen, phenacetin and Cochicine]

**Doses of NSAIDS in Animals**:

Sodium salicylate (orally): Horse & Cattle: 15-120 gm; Sheep, goat & pig: 1-4 gm; Dog: 0.3-1 gm

Aspirin (mg/kg orally): Cattle: 100 twice a day; Horse: 30-40 twice a day; Pig: 10-15 thrice a day; Dog: 10 twice a day; Cat: 10 once in two days.

Phenyl butazone: Dog: 15 mg/kg slow IV once in a day for two days or 20 mg/kg orally twice a day; Cat: 15 mg/kg IV three times a day; Horse: 4 mg/kg orally twice a day; Cattle & Pig: 2-5 mg/kg IV.

Dipyrone: Dog & Cat: 20-25 mg/kg IV, IM or SC; Horse: 5-10 gm IM or IV; Cattle: 50 mg/kg SC, IM or IV.

Meclofenamic acid: Horse: 2 mg/kg/day orally for about a week; Dog & Cat: 2mg/kg/day for about a week.

Naproxen: Horse: 5 mg/kg IV; 10 mg/kg twice a day; Dog: 5 mg/kg orally on first day and at 1-2.5 mg/kg/day during subsequent days.

Acetaminophen: Dog: 25-30 mg/kg orally 3-4 times a day.

Flumixin meglumine: Dog: 1-2 mg/kg orally, IM or IV for 2-3 days; Cat: 1 mg/kg orally for 3-5 days; Horse & Cattle: 1-2 mg/kg orally or IM 1-2 times a day; Pig: 1-2 mg/kg IM once a day.

Ibuprofen: Dpg: 5-10 mg/kg orally once or twice a day.

Indomethacn: Dog: 10 mg/kg/day; Cattle: 1-2 mg/kg/day.

Ketoprofen: Dog & Cat: 1-2 mg/kg/day SC; Horse & Cattle: 2 mg/kg/day IV.

Nimesulide: Dog: 50 mg/dog orally twice a day

**Toxicity of NSAIDs**: Prolonged use may cause gastric bleeding, gastric ulceration or gastric haemorrhages. High doses cause nausea, vomition and CNS excitation in dogs. Cats are more susceptible to aspirin toxicity than other species (slow metabolism and excretion and also deficient in glucuronide conjugation of aspirin). Aspirin should not be used atleast 2 weeks before surgery (haemorrhages due to prevention of platelet aggregation and blood clotting). Phenacetin and paracetamol are contraindicated in cats (cause cyanosis, haemolysis, anaemia, haemoglobinuria and jaundice).

## 4. Other Analgesics

**Xylazine**: Has sedative analgesic and skeletal muscle relaxant effects in all species. Its analgesic effect is due to stimulation of central alpha$_2$ adrenergic receptors and muscle relaxant effect is due to inhibition of excitatory transmission in CNS. Has emetic effect through stimulation of CTZ. It is used to relieve visceral, muscle or joint pains and also as a preanaesthetic. Catecholamines should not be administered in xylazine-treated animals (induction of cardiac arrhythmia). It should not be used to control convulsive seizures as it causes severe CV and respiratory depression and prolongs sedation. Its doses are:

Horse: 0.5–1 mg/kg IV or 1–2 mg/kg IM; Cattle: 0.05– 0.1 mg/kg IV or 0.01 – 0.2 mg/kg IM; Dog & Cat: 0.5 – 1 mg/kg IV or 1 – 2 m/kg IM; Sheep & Goat: 0.05 – 0.1 mg/kg IV; Pig: 2 mg/kg IM; Birds: 5 – 10 mg/kg IM.

# Chapter – 20: CNS STIMULANTS

These drugs are used to counteract the excess depression of CNS caused by over dosage of anaesthetics and in toxicity of CNS depressant drugs or some poisonings. Death under these conditions results from either central respiratory or vasomotor failure or both. Over dosage of CNS stimulants causes convulsions, which can be counteracted by giving anticonvulsants.

**Classification:**
**Medullary Stimulants**: Used for stimulation of depressed medullary respiratory and vasomotor centres (Nikethamide, doxapram and bemegride). The drugs that stimulate respiration mainly by direct stimulation of the medullary respiratory centre are called as **analeptics**.

**Cortical Stimulants**: Used for stimulation of cerebral (sensory) cortex to counteract fatigue or for stimulation of mental activity [Methyl xanthines (Caffeine/aminophylline) and Amphetamines].

**Convulsants**: Spinal Stimulants: These cause convulsive attacks (Pentylenetetrazol, strychnine and picrotoxin).

**Nikethamide (Coramine)**: Acts by directly stimulating the respiratory centre and through increased activity of chemoreceptors of carotid and aortic bodies. Dog: 20-40 mg/kg, IV or IM, repeat if needed after 15-20 minutes.

**Doxapram**: Primarily a respiratory stimulant like nikethamide (relatively more selective on respiratory centre than other analeptics). Dog & Cat: Against barbiturate depression: 5-10 mg/kg IV; inhalant anaesthetic depression 1-1.5 mg/kg IV; Horse: 0.5-1 mg/kg IV.

**Bemegride**: Direct stimulant of respiratory centre. Dog: 15-20 mg/kg IV.

**Caffeine**: An alkaloid obtained from the seeds of *Coffea arabica* and tea leaves (*Thea sinensis*). It has stimulant effect on respiratory and CV systems. It increases sensitivity of respiratory centre to $CO_2$ and direct stimulant effect on resp. centre. It has direct myocardial stimulant effect by increasing the local cAMP levels (inhibition of phosphodiesterase). Its CNS stimulant effects are due to blocking of adenosine action in medulla. Dog: 0.1-1 G hypodermically.

**Aminophylline**: Similar to caffeine. It also relieves the bronchial spasm. Dog: 10 mg/kg IM; Horse: 50 mg orally at 6 hr intervals.

**Amphetamine**: A sympathomimetic having marked CNS stimulant and anoractic effects. In man it is used as cortical stimulant and anoractic agent. Also relaxes the bronchi due to sympathetic actions. Small animals: 1-2 mg/kg sc: Large animals: 100-300 mg/ animal sc.

**Strychnine**: Alkaloid of seeds of *Strychnos nuxvomica*. It is a powerful stimulant of CNS causing severe spinal convusions (convulsive poison). Acts through antagonism of postsynaptic inhibition mediated by glycine in CNS (competitive antagonist of glycine in motoneurons and interneurons in spinal cord).
**Picrotoxin**: It is a nonnitogenous substance obtained from seeds of *Anamirta cocculus* (fish berries). A potent convulsive; acts by antagonism of presynaptic inhibition in CNS mediated by GABA.
**Pentylenetetrazol:** A potent convulsive. It acts through marked reduction in neuronal recovery time resulting in repetitive discharge following a single stimulus; interferes with GABAergic inhibition.
Strychnine, pentylenetetrazol and picrotoxin have no therapeutic use, but used only as experimental pharmacological tools to produce convulsions.

## EXERCISE

1. Classify the CNS transmitters and mention the main physiological function of each one of them.
2. What are the types of mediators of chemical signaling in CNS? Describe the actions of amino acid transmitters.
3. Classify the general anaesthetics? Describe the theories of general anaesthesia anaesthesia.
4. Classify the barbiturates with suitable examples. Describe their pharmacological effects
5. What are inhalation anaesthetics? Give their classification. Descibe the stages of anaesthesia
6. Discusss the structure activity relationship of barbiturates and the advantages and disadvantages of barbiturates anaesthsia.
7. What is premedication? Mention the various objectives of premedication along with what drugs you recommend to achieve each objective.
8. What are tranquilizers? Give their classification and discuss the pharmacology of each group.
9. What are analgesics? Give their classification. Discuss the differences between the classes.
10. What is opium? Describe the pharmacological actions of morphine.
11. What are NSAIDs? Discuss their mode of action and major pharmacological effects.
12. What are antipyretics? Descibe the antipyretic, analgesic and anti-inflammatory actions of salicylates

13. **Write a short note on the following:**
    a) CNS transmitters
    b) Neurotransmitters
    c) Neuromodulators
    d) Neurotrophic factors
    e) Amine transmitters
    f) Amino acid transmitters
    g) Opioid peptides
    h) Neurodegenrative disorders
    i) Theories of general anaesthesia
    j) Stages of anaesthesia
    k) Gaseous anaesthetics
    l) Chloral hydrate
    m) Chlor-Mag anaesthesia
    n) Preanasthetics
    o) Benzodiazepines
    p) Phenothiazines
    q) Tranquilizers
    r) Aniconvulsants
    s) Antidepressants
    t) Analeptics
    u) Surgical anaesthesia
    v) Mood elevators/Thymoleptics
    y) Central muscle relaxants
    w) Why chloroform is not a safe anaesthetic?
    x) Advantages and disadvantages of barbiturates

14. **Differentiate between the following:**
    a) Neuro transmitter & Neuromodlator
    b) GABA & Glycine
    c) Endorphin & Enkephalin
    d) Parkinson's disease & Schizophrenia
    e) Balanced anaesthesia & Basal anaesthesia
    f) General anaesthesia & Local anaesthesia
    g) Thiopenone & Pentobarbitone
    h) Sedative & Hypnotic
    i) Narcotic & Nonnarcotic analgesics
    j) Diclofenac & Nimesulide
    k) Phenanhrene & Benzylisoquinoline alkaloids
    l) Morphine analgesia & Aspirin analgesia
    m) Phenobaritone & Thiopentone
    n) Chloralose & Chloral hydrate
    o) Enflurane & Isoflurane
    p) Premedication & Postmedication
    q) Depression & Mania
    r) Strychnine & Picrotoxin
    s) Rivastigmine & Donepezil

15. **Write the mechanism of action of the following drugs:**
    a) Barbiturates
    b) Diazepam
    c) Nikethamide
    d) Opioids
    e) Morphine
    f) Aspirin (antipyretic)
    g) NSAIDs
    h) Naloxone
    i) Phenylbutazone
    j) Nimesalide
    k) Oxicams
    l) Diclofenac
    m) Xylazine
    n) Lithium carbonate
    o) Methylphenidate
    p) Selegine

16. **Give the therapeutic/clnical uses of the following drugs:**
    a) Barbiturates
    b) Benzodiazepines
    c) Morphine sulfate
    d) Aspirin
    e) Phenylbutazone

17. **What do you mean by the following? Answer in one or two senstences for each of the following:**
   a) Neurotransmitter
   b) Neuromodulator
   c) Neurotrophics
   d) Opioid peptide
   e) Dissociative anaesthetic
   f) Neuroleptanalgesic
   g) Ataractic
   h) Neuroleptic
   i) Antiepileptic
   j) Thymopleptic
   k) Uricosuric agent
   l) Analgesic
   m) Doping
   n) Antigout drug
   o) Addiction
   p) Heroin
   r) Chemical restrain

Sub-P → pain induce

18. **What is the source of the following drugs?**
   a) Strychnine
   b) Picrotoxin
   c) Caffeine
   d) Opium
   e) Morphine

19. **Give the dose and route of administration of the following drugs.**
   a) Thiopentone in dog
   b) Chloral hydrate (hypnotic) in cattle
   c) Ketamine anaesthesia in dog
   d) Atropine as a preanaesthetic in dog
   e) Diazepam (sedative) in dog
   f) Nikethamide in horse
   g) Morphine sulfate in dog
   h) Doxapram in a dog

20. **Matching the pairs:**
   1. Glutamate : Neurotransmitter
   2. Eicosanoids : Neuromodulators
   3. Cytokines : Neurotrophics
   4. Ach choline : Amine transmitter
   5. Glutamate : Amino acid transmitter
   6. GABA : Inhibitory transmitter
   7. Glycine : Inhibitory transmitter
   8. Glutamate : Excitatory transmitter
   9. Asparatate : Excitatory transmitter
   10. Adenosine : Purine
   11. β–Endorphin : Opioid peptide
   12. Substance P/Eledoisin : Tachykinins
   13. Substance P : Pain inducer
   14. Melatonin : Circadian rhythm
   15. Prostaglandins : Eicosanoids
   16. 5-HT : Hallucinations
   17. Haloperidol : Dopa antagonist
   18. α–Bungarotoxin : ACh antagonist
   19. Bromocriptine : Dopa agonist
   20. Apomorphine : Dopa agonist
   21. Epibatidine : Nicotinic agonist
   22. NMDA : Glutamate agonist
   23. AMPA : Glutamate agonist
   24. Ketamine : Glutamate antagonist
   25. Diazepine : GABA agonist
   26. Barbiturate : $GABA_A$ agonist
   27. Baclofen : $GABA_B$ agonist
   28. Strychine : Glycine antagonist
   29. Bicuculline : GABA antagonist
   30. Caffeine : Adenosnine antagonist
   31. NO : cGMP formation
   32. $N_2O$ : Priestly
   33. $N_2O$ : Laughing gas
   34. Ether anaesthetic : CW Long
   35. Ether dome : WTG Morton
   36. Anaesthesia : OW Holmes
   37. Chloroform : JY Simpson
   38. Althesin : Steroid anaesthetic
   39. Urethane : Lab animal anaesthsia
   40. Primidone : Prodrug
   41. Doxapram : Respiratory stimulant
   42. Strychnine : Convulsant
   43. COX 1 : Constituent enzyme
   44. COX 2 : Inducible enzyme
   45. Codeine : Phenanthrene alkaloid
   46. Iproniazid : MAO inhibitor
   47. Fluoxetine : 5-HT uptake inhibitor
   48. Mania : Carbamazepine/Lithium carb.
   49. Nikethamide : Medullary stimulant
   50. Cortical stimulant : Caffeine
   51. Spinal stimulant : Pentylene tetrazol/Strychnine
   52. Mefenesin : Central muscle relaxant
   53. Parkinson's disease : Dopamine deficiency
   54. Alzhemier disease : Cholinergic deficiency
   55. Papaverine : Benzylisoquinoline alkaloid
   56. Impipramine : Tricyclic antidepressant
   57. Nonselective COX inhibitors: Salicylates/Propionic acid derivatives/Phenylacetic acid derivatives/ Paraaminophenol derivatves/Pyrozolan derivatives.
   58. Low to moderate COX-2 inhibitors: Oxicams/Indomethacin/ Nimesulide/Etodolac/Celecoxib
   59. Highly selective COX-2 inhibitors: Rolecoxib/Deracoxib

60. Schizophrenia/Mania : Excess dopaminergic activity in limbic system
61. Flumazenil : Benzodiazepine antagonist
62. Zonisamide : Sulfonamide-based antiepileptic
63. Eledoisin : Peptide of Mediterranean octopus
64. Depression : Monoaminergic deficiency in limbic system
65. Depression : MAO inhibitors/Tricyclic antidepressants
66. Benzodiazepine with acive metabolite: Chlordiazepoxide/Desmethyldiazepam/Diazepa/Flurazepam
67. Long-acting benzodiazepine: Chlordiazepoxide/Desmethyldiazepam/Diazepa/Flurazepam
68. Zolpidem: Not a benzodiazepine. but acts like benzodiazepine derivatives
69. Antimaniac drug: Carbamazepine/Valproic acid/L-Amotrigine/Gabapentin/Vigabatrin/Trgabine
70. Antidepressant drug: Amoxapine/Mitrazapine/Nefazodone/Trazodone/Maprotiline
71. Selective 5-HT reuptake inhibitor: Fluoxetine/Citalopram/Reboxitine/Sertaline/Paroxetine
72. Selegeline/Amantadine/Antimuscarinic drug (Biperidin/Procycline/Trihexyphenidyl): Antiparkinsonian drug
73. Antiparkinsonian antimuscarinic drug: Biperidin/Procyclidine/Trihexyphenidyl
74. St.John's wort: MAO inhibitor
75. *Hypericum perforatum*: Antidepressant
76. *Hypericum perforatum*: MAO inhibitor
77. Parkinson's disease: Imbalance between dopamine and ACh in nitrogastriatal tract of brain.
78. Alzheimers disease: Increase in cholinergic activity in cerebral cortex and limbic system
79. Alzheimers disease: Rivastigmine/Donepezil
80. Rivastigmine/Donepezil is used to treat Alzheimer disease.
81. COMT inhibitor: Tolcapone
82. Opioid antagonist: Naloxone/Naltrexone/Nalmefene
83. Difenoxin: Meperidine-like opiate
84. Propxyphene: Derivative of methadone
85. Strong opioid agonist: Morphine/Heroin/Meperidine/Methadone/Fentanyl/Supentanil
86. Moderate opioid agonist: Codeine/Prophoyphene
87. Mixed opioid agonist-antagonist: Pentazocine
88. Partial opioid agonist: Buprenorphine
89. Pentazocine: Agonist to kappa and sigma receptors/Weak antagonist to mu and delta receptors
90. Antigout Drug: Allopurinol/Probenecid/Sulfinpyrazone/Acetaminophen/Pheneacetin/Colchicine

21. **What drug you recommend for the following purposes? Mention its dose and route of administration.**
    a) Preanaesthetic anticholinergic in a dog.
    b) Preanasthetic sedative in a cat/dog/horse.
    c) General anaesthesia for 30 min in a cat/dog/horse.
    d) General anaesthesia for 30 min a pregnant bitch.
    e) Inhalation anaesthesia in a horse.
    f) General anaesthesia in a cock.
    g) Analgesic in a dog/horse.
    h) Cough sedative in a dog.
    i) Severe diarrhea in a dog.
    j) Spasmodic colic in a horse.
    k) To immobilize a lion
    l) Arthritis in a bullock.
    m) To mask lameness in a horse.
    n) Joint pain in a bullock.
    o) Respiratory depression in a horse.
    p) Respiratory depression due to overdosage of anaesthetics in a dog.

21. **Give the most appropriate reason for each of the following statements**:
    a) General anaesthesia is not generally followed in an adult bullock/buffalo.
    b) Anaesthetics cause loss of pain sensation.
    c) Deep surgical anaesthesia is not usullay recommended for surgical operations.
    d) The dose of d-TC should be reduced to about one-third before ether anaesthesia.
    e) Catecholamines are contraindicated in halothane anaesthesia.
    f) Barbiturate anaesthesia is not suitable for cesaerean section.
    g) Thiopentone should not be injected SC or IM.
    h) Chloral hydrate is a better hypnotic than a general anaesthetic.
    i) Morphine causes simulated vomition in a spinal dog.
    j) Morphine premedication is contraindicated in cyclopropane anaesthesia.
    k) Morphine is used to treat chronic diarrhea in dogs.
    l) Thiopentone action is terminated by redistribution.

m) Anaesthetics cannot be used as analgesics.
n) Prolonged use of barbiturates is not recommended
o) Prolonged use of barbiturates increases their own metabolism.
p) Hypnotics/sedatives as preanaesthetics help in smooth induction of anaesthesia.
q) Hpnotics/sedatives as preanaesthetics minimize toxic effects of anaesthetics.
r) Chlorpromazine can be used as an antiemetic
s) Phenothiazine derivatives can be used to prevent motion sickness.
t) Adrenaline is contraindicated in chlorpromazine or haloperidol-pretreated animals.
u) Phenothiazine tranquilizers are to be avoided in feedlot livestock (before slaughter).
v) Morphine is contraindicated in strychnine convulsions in a dog.
w) Morphine should not be used to treat strychnine convulsions in a dog.
x) Chloral hydrate is a prodrug.
y) Codeine acts as a potent antitussive.
z) Thymol is added to halothane.
a`) Morphine causes anuria.
b`) Phenylbutazone is a prodrug.
c`) Phenylbutazone is used in gout.
d`) Phenylbutazone is a dope drug.
e`) Primidone is a prodrug.
f`) Caffeine overcomes drowsiness.
g') Tetanus toxin causes convulsions.
h') Phenylbtazone is contraindicated in animals with CHF.
i') Adenosine exerts protective action in CNS.
j') Catecholamines are contraindicated in xylazine-treated animals.
k') Droperidol-fentanyl combination is not used in ruminants.
l') Morphine conjugates are pharmacologically active.
m') Beta-endorphin and enkephalins are called opioid peptides.
n') Melatonin can be used to overcome 'jet lag'.
o') Melatonin may be used to enhance performance of night-shift workers.
p') Size of bird's pupil is not altered by morphine.
q') Catecholamines should not be used before or duing xylazine anaesthesia.
r') Ether/Halothane is not used in aminoglycoside antibiotic treated animals.
s') Phenothiazine tranquilizers can be differentiated from sedatives.
t') Aspirin therapy must be discontinued before surgery.
u') Pethidine can be used in intestinal colic.
v') Ether should not be exposed to moisture.
w') Diclofenac causes gastric haemorrhages.
x') Diacetylmorphine has no clinical use.
y') Chloroform is not a safe anaesthetic.
z') Nitric oxide promotes cGMP formation.
aa) Diazepam is not recommended as oral therapy for emergency control of convulsions.
bb) Phenothiazine derivatives should not be used in treating epilepsy.
cc) Xylazine is not used to control convulsive seizures in dogs.
dd) Misoprostal (PG $E_1$ analog) is recommended along with therapy of NSAIDs.
ee) Benzodiazepine is an inactive prodrug.
ff) Chlorzepine/Desmethyldiazepam/Oxazepam is a prodrug.
gg) Chlordiazepoxide/Desmethyldiazepa/Diazepam/Fkurazepam has long half-life.
hh) Carbamazepine/Valproic acid/L-Amotrigine/Gabapentin/Vigabatrin/Trgabine is used in mania.
ii) Amoxapine/Mitrazapine/Nefazodone/Trazodone/Maprotiline is used as an antidepressant.
jj) Lithium carbonate/Valproic acid/Gabapentin is used as antidepressant
kk) Selegeline/Amantadine/Antimuscarinic drug (Biperidin/Procycline/Trihexyphenidyl)/Tolcapone is used in treat Parkinson's disease.
ll) Biperidin/Procycline/Trihexyphenidyl is beneficial in Parkinson's disease.
mm) Diphenoxylate is preferred to meperidine as analgesic or antidiarrhoeal
nn) Sgma receptors are not true oipoid receptors/Sigma receptors are not oipoid specific

# Chapter – 21: PHARMACOLOGY OF SOMATIC NERVES

## 1. Local Anaesthetics

Cause reversible loss of sensation of a particular area or region of the body, without causing loss of consciousness. Local anaesthetics are injected in the vicinity of nerves for localized desensitization (nerve blocks). An ideal local anaesthetic should not be irritant to the tissues, should have long duration of action and should not have systemic effects (on CNS, CVS or respiratory and gastrointestinal systems).

**Mode of Action**: Prevent conductance of painful impulses through nerves by preventing depolarization as a result of blockade of sodium ion permeability through nerve axonal membrane.

**Potentiation of Local Anaesthetic Action**:

a) **By decreasing the absorption of injected local anaesthetic**: Addition of adrenaline to local anaesthetic solution at 1:1.00,000 to 1:50,000 dilutions, which causes constriction of blood vessels in the area and thus reduce the absorption of local anaesthetic.

b) **By increasing the spread of injected local anaestheticb** Addition of hyaluronidase increases the diffusion or spread of the local anaesthetic solution in the area.

**Local Anaesthetic Agents**:

a) **Cocaine:** It is the mother of local anaesthetics. Alkaloid of leaves of *Erythroxylon coca*. Due to its marked CNS stimulant property it is not used in clinical surgery.

b) **Procaine**:

| Local Anaesthesia Type | Small Animals | Large Animals |
|---|---|---|
| Infiltration | 1% solution | 2% solution |
| Conduction block | 2% solution 2.5 ml | 4% solution 5-10 ml |
| Epidural | | 2% solution |

c) **Lidocaine**: 1-2% sol. For epidural, nerve block anaesthesia. Also used at 2 mg/kg IV at 20 min interval to control cardiac arrhythmia in dogs.

d) **Hexylcaine**: 5, 1 and 1-2% solution for topical. infiltration and epidural anaesthesia respectively.

e) **Tetracaine**: For topical anaesthesia in eye (0.5-1% solution)

**Ethyl Chloride**: Surface anaesthetic to be used on skin. Evaporates very rapidly and freezes the areas and makes the skin insensitive for a brief period.

**Regional Anaesthesia (Intrathecal or spinal and Epidural Anaesthesia)**: Commony used in large animals in combination with hypnotics or neuroleptanalgesics. (General Anaesthesia is not usually recommended in large animals).

**Systemic Effects of Local Anaesthetics**: If absorbed in sufficient amounts cause CNS excitation (restlessness, tremors or convulsions) neuromuscular or ganglionic blockade, myocardial depression and antispasmodic effect on intestines.

**Toxicity of Local Anaesthetics**: Injection at high concentration results in absorption causing CNS neurotoxicity (excitement, tremors and convulsions), followed by depression.

## 2. Skeletal Muscle Relaxants (Including Central Muscle Relaxants)

These drugs cause relaxation of skeletal muscles and used as adjunct to anaesthetics before surgery or in therapeutic management of abnormal muscle function.

**Classification**: Based on site of action as

**A. Central Acting**: Mefenesin, guiafenesin, diazepam, baclofen, methocarbamol, carisoprodal and chlorzoxazone.

**B. Peripherally Acting**: These are always given by IV injection.

a) **Neuromuscular Blockers** (NMBs): Two types:

1. Competitive Neuromuscular Blockers (curariform drugs): **Natural**: d-Tubocuraine (alkaloid of leaves of *Chondrodendron tomentosum*, South American arrow poison: Potcurare, tubocurare, calabash curare) and **Synthetic**: Alcuronium, atracuronium, pancuronium, rocuronium, beta erythroidine and gallamine.
2. Noncompetitive Neuromuscular Blockers: Decamethonium and succinylcholine (suxamathonium).

b) **Direct Skeletal Muscle Relaxant**: Hydantoin derivatives: Dantrolene and phenytoin.

**Centrally Acting**: These are also called skeletal muscle spasmolytics, act through by interfering with internuntial pathways in spinal cord and reticular activating system. These are given either orally or parenterally.

**Mefenesin and Guaiafenesin**: Act as glycine agonists and thus antagonize strychnine or tetanus convulsions, but not those of picrotoxin or pentylenetetrazol (GABA antagonism). Guaiafenesin has wide margin of safety and used 5% in 5% dextrose as IV infusion in horses for casting.

Dose: Guiafenesin: Dog: 45-90 mg/kg IV; Large animals: 6o-120 mg/kg IV.

**Diazepam**: Causes paralysis of muscles through GABA facilitation (see above), and thus antagonizes convulsions of picrotoxin or nikethamide. Dog: 0.5-1 mg/kg IV or IM. Cat: 2.5-5 mg/kg orally, thrice a day.

**Baclofen**: $GABA_B$ agonist. Causes paralysis of muscles by inhibition of motor neurons in spinal cord.

**Methocarbamol**: Mechanism of action unknown. Used in tetanus and strychnine poisoning. Dog & Cat: 45 mg/kg IV; Horse: 5-20 mg/kg IV. It is chemically related to guaiafenesin; also has CNS depressant (causes sedation: Dog & Cat: 40 mg/kg IV).

**Competitive NMBs**: Also called as Nondepolarizing NMBs:

Act by competitive antagonism of ACh for nicotinic receptors at neuromuscular junction. Do not allow ACh to cause depolarization of muscle fibres, hence called as nondepolarizing neuromuscular blockers. These cause flaccid paralysis of the skeletal muscles (curariform effect). The order of paralysis of muscles is eyes first followed by neck and mscle, limbs and lastly the diaphragm. The muscle paralysis lasts for about 30 – 60 min. Curariform drugs cause hypotension through histamine release, but don not cross the blood-brain-barrier or placenta. These drugs are not absorbed from GIT or metabolized in liver and excreted unaltered through urine and bile.

The curariform effect is potentiated by quinidine, anaesthetics (barbiturates, halothane, methoxyflurane and ether) and many antibiotics (aminoglycosides, tetracyclines, polmyxins and lincosamides). The effect can be overcome by AntiChE agents like neostigmine (0.03-0.05 mg/kg IV), pyridostigmine (0.25 mg/kg IV) and edrophonium (0.12 mg/kg IV). The antiChEs must be given with concurrent atropine injection (0.025-0.05 mg/kg IV) to counter excessive muscarinic effects of antiChEs.

**Noncompetitive NMBs**: Also called as Depolarizing NMBs:

Act through persistent depolarization of postsynaptic muscle fibre (bind to postjunctional cholinergic nicotinic receptors) and make it nonresponsive to ACh released from the motor nerve. These do not compete for acetyl choline nicotinic receptors at the motor end plate. The paralysis caused by these drugs is preceded by muscular fasciculations/twitchings. Following IV injection of succinylcholine muscle paralysis occurs within a min and it lasts for a short duration (5-15 min) because of its inactivation by pseudoChE in plasma and liver. The drug may also induce cardiac arrhythmia and cause cholinergic effects (muscarinic and nicotinic). Concurrent exposure to OP compounds (antiChEs) potentiates the action of succinylcholine.

| Differences between | Competitive NMBs and | Noncompetitive NMBs |
|---|---|---|
| 1. Action at motor end plate: | No depolarization | Persistent depolarization |
| 2. Initial effect on muscles: | No effect | Transient fasciculations |
| 3. Type of muscle paralysis: | Flaccid | Tonic |
| 4. Effect of AntiChE agents: | Antagonism | Synergistic effect |
| 5. Species Sensitivity: | Rat > Rabbit > Cat | Cat > Rabbit > Rat |

**Doses and Administration of Neuromuscular Blockers:**

| DRUG | Dose & Route of Administration (mg/kg; IV) | | | | | |
|---|---|---|---|---|---|---|
| | Dog | Cat | Pig | Cattle | Sheep | Horse |
| d-Tubocurarine | 0.5 | 0.5 | 0.25 | Calf:0.05 | Lamb:0.05 | |
| Gallamine | 1.0 | 1.0 | | Calf: 0.5 | Lamb: 0.5 | 0.5-1.0 |
| Succinylcholine | 0.2-1 | | 2.0 | 0.01-0.02 | | 0.10-0.20 |
| Alcuronium | 0.5 | | | | | |
| Atracuronium | 0.1 | | | | | |
| Pancuronium | 0.5 | | | | | |

**Dantrolene and Phenytoin:**

Dantrolene acts directly on the skeletal muscle fibres. It inhibits the excitation-contraction coupling mechanism by interfering with release of calcium ions from sarcoplasmic reticulum in the muscle fibres, but has no effect on smooth or cardiac muscles. Phenytoin in addition to the actions of dantrolene is also believed to act through ineference of transmitter function of ACh at motor end plate. Dantrolene: Horse: 15-20 mg/kg, by slow IV; Pig: 2.5-5 mg/kg, IV.

**Therapeutic Uses of Neuromuscular Blockers/Skeletal Muscles Spasmolytics:**

a) As preanaesthetic before for inducing skeletal muscle relaxation (adjuncts to general anaesthesia).
b) For control/restraint and capture of ferocious wild animals (curariform drugs: capture/dart guns)
c) As anticonvulsants. Methocarbamol for control of tetanus or strychnine convulsions.
d) For orthopedic surgical manipulation (diazepam or methocarbamol IV).
e) Adjunct therapy in attending acute muscle injuries (centrally acting drugs).
f) Prevention or treatment of malignant hyperthermia or rhabdomyolysis in horses or other species and porcine stress syndrome (dantrolene and phenytoin).

Cobra snake venom contains highly potent neuro toxins **α-Bungarotoxin** and **β-Bungarotoxin** which cause paralysis of skeletal muscles (including intercostals and diaphragm: failure of respiration) by binding to the nictonic ACh receptors and inhibiting ACh release from motor nerve endings respectively. The Clostridial toxin **botulinum toxin** also causes skeletal muscle paralysis by preventing ACh release from the motor nerve endings.

**EXERCISE**

1. What are neuromuscular blockers? Give their classification and explain their mechanisms of action and clinical uses.
2. What are local anaesthetics? Explain their mechanism of action and discuss how you potentiate their action.
3. What are muscle relaxants? Give their classification. Explain their mechanisms of action and give their clinical uses.
4. **Write short notes on the following:**
   a) Potentiation of local anaesthesia.
   b) Regional/epidural anaesthesia.
   c) Central muscle relaxants.
   d) Competitive NMBs.
   e) Depolarizing NMBs
5. **Differentiate between the following:**
   a) dTC & Succinylcholine
   b) Dantrolene & diazepam
   c) Competitive & Noncompetive NMBs
   d) Depolarizing & Nondepolarizing NMBs
   e) Central & Peripheral muscle relaxants
   f) dTC & Diazepam/Mefenesin
   g) Local & General anaesthesia
   h) Local & Regional Anaesthesia
   i) Epidural & Spinal anaesthesia
   j) Phenytoin & Methocarbamol
   j) Topical & Inflitration anaesthesia

6. **What drug you recommend for the following purposes:**
   a) Topical anaesthesia in eye.
   b) Infiltration/conduction anaesthesia in a bullock.
   c) Nerve block anaesthesia in a buffalo.
   d) Epidural anaesthesia in a cow.
   f) Rumenotomy operation in a bullock.
   g) Capture of ferocious animals.
   h) Preanaesthetic muscerelaxant in a dog.
   i) To control tetanus convulsions in horse/cat.
   j) Malignant hyperthermia in a horse.
   k) Porcine stress syndrome.

7. **Give the most appropriate reason for each of the following statements:**
   a) Ethyl chloride is used as a surface anaesthetic.
   b) Cocaine is regarded as mother of local anaesthetics.
   c) Adrenaline increases duration of local anaesthesia.
   d) Hyaluronidase increases area of anaesthetization.
   e) Cocaine is not used clinically as local anaesthetic.
   f) Dantrolene is used in malignant hyperthermia in horses.
   g) dTC is a competitive neuromuscular blocker.
   h) Decamethonium is a depolarizing neuromuscular blocker.
   i) Mefenesin/Baclofen/Diazepam is a central muscle relaxant.
   j) Curarifirm drugs cause hypotension.
   k) Muscle paralysis by succinylcholine precedes muscular fasciculations.
   l) AntiChEs reverse curariform effect.
   m) The muscle paralysis of succinylcholine lasts for a very short period.
   n) Curariform drugs do not cause centrally-mediated muscle paralysis.
   o) Dantrolene is functionally different from other peripheral muscle relaxants.
   p) Caution must be exercised while administering curarifirm drugs in animals treated with ether/halothane/quinidine/aminoglycosides/polymyxins/lincosamides/tetacylines.
   q) Edrophonium reverses neuromuscular blockade of dTC.

8. **What is the source of the following drugs:**
   a) Cocaine
   b) d-Tubocurarine

9. **What do you mean by the following:**
   a) Tube curare
   b) Pot curare
   c) Spinal anaesthesia
   d) Epidural anaesthesia
   e) Malignant hyperthermia
   g) Arrow poison
   h) Dart gun

10. **What are clinical uses of muscle relaxants/muscle spasmolytics?**

11. **Explain the mechanism of action of the following drugs:**
   a) d-Tubocurarine
   b) Pancuronium
   c) Decamethnium
   d) Succinylcholine
   e) Diazepam
   f) Baclofen
   g) Mefenesin
   h) Procaine
   i) Dantrolene
   j) Phenytoin
   k) Methocarbamol
   l) Alcuronium
   m) Lidocaine
   n) Ethyl chloride

12. **Matching the pairs:**
   a) Gallamine : Curariform drug
   b) Dantrolene : Acts on muscle
   c) Atracuronium : Nicotinic receptor antagonism
   d) Mefenesin : Central muscle spasmolytic
   e) Succinylcholine : Depolarizing NMB
   f) Decamethonium : Noncompetitive NMB
   g) d-Tubocuraine : Nondepolarizing NMB
   h) Methocarbamol : Central muscle relaxant
   i) Diazepam : Central muscle relaxant
   j) Muscle relaxants : Tetanus/Strychnine convulsions
   k) Depolarizing NMB : Potentiated by AntiChEs
   l) Competitive NMB : Reversed by AntiChEs
   m) Alpha-bungarotoxin : Blocks nACh receptors
   n) Beta-bungarotoxin : Blocks ACh release from motor nerve terminals
   o) Botulinum toxin : Blocks ACh release from motor nerve terminals

# SECTION: IV: SYSTEMIC PHARMACOLOGY

## Chapter – 22: DRUGS ACTING ON DIGESTIVE SYSTEM

### 1. Sialagogues

Drugs which increase the volume and fluidity of saliva (Sialics) and help in improving appetite and digestion of food.

**Classification**: Based on pharmacological action.

A. **Reflex Sialagogues**: Increase salivation through reflex action.
   1. **Simple Bitters**: Gentian (Horse and Cattle: 2 – 10 gm; Sheep and Goat: 0.5 – 1.5 gm; Swine: 0.5 – 1 gm orally) and Quassia.
   2. **Alkaloidal Bitters**: Nuxvomica (Horse: 2-4 gm; Cattle: 4-8 gm; Sheep and Goat: 1-1.5 gm; Swine: 0.5-1 gm).
   3. **Nauseating and Emetic Bitters:** Ipecacuanha.

B. **Cholinergic Sialagogues**: Arecoline, Physostigmine and Neostigmine (cholinergic-muscarinic action).

C. **Direct Sialagogues**: Stimulate the salivary gland: Iodine.

**Antisialagogues**

Drugs which decrease formation and fluidity of saliva and cause dryness of mouth (Antisialics): Atropine and Hyoscine. Used as preanaesthetics to reduce salivary and bronchial secretions.

### 2. Stomachics

Drugs which increase functional activity of stomach by increasing gastric motility and secretion.

**Classification**: Based on mechanism of action.

A. **Cholinergics Agonists**: Increase GIT motility through cholinergic-muscarinic action.

B. **Dopaminergic Antagonists**: Dopamine decreases GIT motility. Dopamine antagonism increases GIT motility: Metoclopramide (see prokinetics).

C. **Alkaline Stomachics**: Bicarbonate salts.

D. **Histaminergics**: Increase gastric acid secretion and GIT motility: Betazole (histamine analog) is used to detect achlorhydria or hypochlorhydria.

**Vegetable Stomachics**: Nuxvomica, gentian and ginger (Horse and Cattle: 15-60 gm; Sheep and Goat: 5-10 gm; Swine: 2-5 gm; Dogs: 0.5-1 gm)

**Antistomachics (Gastric Sedatives)**: Drugs which decrease gastric hyperacidity and motility.

**Classification**: Based on mechanism of action.

A. **Antimuscarinic Drugs**: Atropine and its analogs.

B. **Antispasmodics** : Relax the GI smooth muscles: Pethidine

C. **$H_2$ Receptor Blockers**: Block histamine-induced gastric acid secretion: Cimetidine, ranitidine, famotidine etc.

### 3. Carminatives

Are drugs which prevent formation of gases and help in their expulsion from GIT; used in case of flatulence.

A. **Volatile Oils**: Turpentine oil (Hose: 60 ml; Cattle: 120 ml), Eucalyptus oil (Horse: 4-16 ml; Dog: 0.5-1.5 ml) as emulsion

B. **Volatile solids**: Camphor and Menthol

C. **Volatile Anaesthetics**: Ether and Chloroform.

D. **Tr. Asafoetida**: Horse: 15-60 ml; Dog: 0.5-1.5 ml.

### 4. Emetics and Antiemetics

Emetics are the which cause vomiting in animals and are capable of vomiting; help in removal of ingested poisons. Generally emetics are commonly used in cats or dogs.

**Classification**: Basing on mechanism of action.

A. **Central Emetics**: By stimulating the medullary emetic centre directly or through CTZ. Stimulation of vestibular apparatus and activation of vestibular nuclei (motion sickness) also induce vomiting stimulating emetic centre via CTZ, which is stimulated by dopamine, histamine, $\alpha_2$ agonists and 5-HT.
   a) **Apomorphine**: A derivative of morphine, a dopamine agonist. Being a morphine derivative it causes CNS excitation in cats. Dog: 3-5 mg/kg orally, 0.02 mg/kg IV or 0.25 mg/kg SC.
   b) **Xylazine**: A central $\alpha_2$ adrenoceptor agonist; causes sedation and hypotension. Cat: 0.3-0.5 mg/kg IV or IM.

B. **Reflex or Peripheral Emetics**: Irritate pharynx or gastric mucosa stimulating vagus or visceral afferent nerves reflexly stimulating the emetic centre: Inorganic salts: Sodium chloride, sodium carbonate or copper sulfate (about 5 gm into pharynx), and hydrogen peroxide.
   Dog: Salts: 5-10 gm into pharynx, $H_2O_2$ 5-10 ml orally.

C. **Mixed Action (Both central and peripheral)**: Ipecac contains an alkaloid emetine which acts on CTZ and also irritates gastric mucosa. Syrup of ipecacuanha. Dog: 2.5- 5 ml/kg orally.

**Contraindications of uses of emetics**:

A. Ingestion of corrosive poisons.
B. CNS stimulant toxicity.
C. Unconscious animals.
D. Opium poisoning.

**Antiemetics**

Are drugs which suppress vomiting or abolish the sensation of vomition. Commonly used in cats and dogs.

**Classification**: Basing on mechanism of action. The antiemetics block stimulation of emetic centre or CTZ or both.

A. **Anticholinergic Drugs**: Atropine like antimuscarinic alkaloids: Isopropamide, Hyoscine/Scopolamine,. These act either peripherally by blocking stimulation of visceral afferent nerves (glycopyrrolate and propantheline) or by preventing stimulation of emetic centre or CTZ by cholinergic visceral afferent nerves (atropine, hyoscne/scopolamine).
   Isopropamide and Propanthilene: 0.25 – 1 mg/kg orally twice or thrice a day.

B. **Phenothizine Tranquilizers**: Main antiemetic effect is mainly due to central antidopaminergic action (on CTZ) and partly due to antihistaminic and anticholinergic effects. Doses in dogs are:
   Aceprcmazine: 0.025-0.25 mg/kg SC, IV or IM.
   Chlopromazine: 0.25 – 0.5 mg/kg SC, IM or IV 3 or 4 times a day.
   Prochlorperazine: 0.1 mg/kg IM 2 0r 3 times a day.

C. **Antihistamines ($H_1$ antagonists)**: Act by interfering vestibular stimulation of emetic centre by cholinergic and histaminergic afferent nerve pathways; also cause sedation.
   Dimemhydrinate, Diphenhydramine, Cyclizine, Meclizne and Promethazne: 2-8 mg/kg orally twice or thrice a day.

D. **Antidopaminergics**: Metoclopramide exerts antiemetic effect through inhibition of central dopaminergic transmission and 5-HT antagonism in CTZ, and peripherally by promoting gastric and upper duodenum emptying. Dog: 0.1 – 0.5 mg/kg orally, SC or IM twice or thrice a day.

E. **Antiserotonergics**: Ondansetron and dolasetron act by antagonizing the peripheral and central actions of 5-HT by inhibiting 5-$HT_3$ receptors on visceral vagal nerve terminals and in CTZ. Dog: Ondansetron: 0.1 – 0.2 mg/kg orally 2 or 3 times a day; Dolasteron: 0.5 mg/kg IV once a day.

**5. Cholagogues**

Drugs which stimulate the contractions of gall bladder and increase bile flow (Cholekinetics) into the duodenum by relaxing the sphincter oddi.

A. Podophyllum: Dried rhizome and root of *Podophyllum palmatum, P. emodi* and *P. hexandrum*: Horse : 5-10 gm; Dog: 0.1 – 0.2 gm orally.
B. Mercurous chloride (calomel): Horse and Cattle: 4 – 8 gm; Dog: 50 – 250 mg orally.

C. Cholinergic Drugs
D. Cholesysokinin: Secreted by duodenal mucosa; physiological stimuli in increasing bile flow.
E. Cerutide/Caerulin (a decapeptide from frog skin) has cholesystokinin action

**Choleritics**

Drugs which increase formation of bile in hepatocytes. Bile helps in absorption of dietary fats and vitamins: Bile salts: Sodium tauroglycocholate, potassium glycholate, dehydrocholic acid or sodium dehydrocholate (Dog: 0.2 – 0.4 gm). Oxybutyric acid derivatives: Clanobutin and cronebile are usd in livestock.

## 6. Intestinal Astringents

Are drugs which help in forming a protective layer and exert protective action on intestinal mucosa against the irritants by precipitating the proteins in the mucosa. These agents also prevent sensory nerve irritation in intestinal mucosa and are used in enteritis and diarrhoea.

A. **Tannic acid**: Horse: 4 – 8 gm; Cattle: 10 – 20 gm; Sheep and Goat: 2 – 3 gm; Swine: 1 – 1.5 gm; Dog: 0.5 gm orally.
B. **Catechu** along with ginger, chalk and creta as astringent powder in cattle.
C. **Aluminum hydroxide gel**: Also acts as an antacid and demulcent. Dog: 2 – 4 ml orally.

**Intestinal Adsorbents**: These agents help in prevention of absorption of toxicants by adsorbing the toxicants and reducing intestinal secretions. Used in diarrhea: Kaolin and bismuth carbonate.

## 7. Appetizers

These drugs promote appetite; used to overcome anorexia in animals. The drugs used in arorectic animals are

A. **Glucocorticoids**: Appetite is increased due to euphoria (antistress). Prolonged use causes catabolic effect (promotion of gluconeogenesis through beakdown of muscle protein). Prednisone @ 1 mg/kg orally on alternate days.
B. **Anabolic steroids**: Increase appetite and promote erythropoiesis and weight gain (anabolic effect). These are not to be used in CHF (sodium and water retention); antagonize catabolic action of glucocorticoids. Stanozolol @ 0.25 mg/kg/day orally or 2.5 – 10 mg/kg IM every 7 days.
C. **5-HT antagonists**: Block 5-HT receptors and antagonise the stimulatory action of 5-HT on the hypothalamic satiety centre; also stimulate GH secretion. Cyproheptadine: Cat: 1-5 mg orally twice a day.
D. **Benzodiazepines**: Inhibit satiety centre by GABA antagonism. Diazepam/Oxazepam: 1 – 2mg/kg orally once or twice a day.

## 8. Anorexigenics

Drugs which reduce appetite by inhibiting the hypothalamic satiety centre, exert anorectic effect and are used to treat obesity in men and women.

A. **Centrally Acting Sympathomimetics**: Amphetamine (sympathomimetic with strong CNS stimulant activity) and its derivatives (dextroamphetamine), mephenteramine and mazindol.
B. **By Facilitating Central 5-HT Action**: By increasing release and reducing uptake of 5-HT: Fenfluramine; By reducing 5-HT uptake: Fluoxetine; By inhibiting uptake of both 5-HT and NorA in CNS: Sibutramine

## 9. Antacids

These are basic agents neutralizing gastric hyperacidity; used to treat gastric acidity in mono-gastric animals and ruminal lactic acidosis in ruminants. The antacids are not absorbed and act by converting the gastric acid to neutral salt and water. Antacids also promote local production of prostaglandin: $PGE_1$, which exerts cytoprotective action on gastric mucosa by preventing gastric acid secretion.

a. **Systemic antacid**: Sodium bicarbonate: Affectssystemic acid base balance; produce acid rebound by releasing $CO_2$.

b. **Nonsystemic antacids**: These do not significantly affect systemic acid base balance:
Magnesium hydroxide: Cattle: 100-300 gm; Sheep: 10-30 gm.
Magnesium carbonate: Cattle: 10-80 gm; Sheep: 2-10 gm.
Aluminum hydroxide: Cattle: 30 gm; Dog: 100-200 mg; Cat: 50-500 mg.
Calcium carbonate: Horse: 30-60 gm; Cattle: 60-360 gm; Sheep and Goat: 8-16 gm; Swine: 10-15 gm; Dog: 0.5-5 gm.
Magnesium oxide: Foals and Calves: 2-12 gm.

## 10. Antiulcer Drugs

These are drugs used to treat gastric ulceration induced by gastric hyperacidity. Gastric ulceration in man has been attributed to *Helicobacter* bacteria, but its role in domestic animals needs to be studied. The antiulcer drugs are classified basing on their mode of action as below:

A. **Antacids**: By neutralizing gastric acid (see above).
B. **Histamine Antagonism**: $H_2$ Receptor Antagonists: Histamine increases gastric acid secretion by the parietal cells. $H_2$ antagonists block gastric acid secretion (see antihistaminics). The doses of $H_2$ antagonists are:
Cimetidine: Dog: 5-10 mg/kg orally 3-4 times a day orally; Horse: 15-20 mg/kg twice a day orally.
Ranitidine: Dog: 0.5 mg/kg SC, IV or orally twice a day; Horse: 1-1.5 mg/kg IV 10 mg/kg orally twice a day.
Famotidine: Dog: 1 mg/kg/day orally or IV; Horse: 2-4 mg/kg orally or 0.2-0.4 mg/kg IV twice a day.

C. **Cytoprotective Effect on Gastric Mucosa**:
   a. Sucralfate: It is not absorbed in stomach; in gastric acid medium it breaks to sucrose octasulfate and aluminum hydroxide. Acid is neutralized by aluminum hydroxide. Sucrose octasulfate polymerizes to a viscous substance which forms a protective coat over the ulcerated gastric mucosa and also prevents back diffusion of $H^+$. Sucralfate also promotes $PGE_1$ formation and release.
   Sucralfate: Dog: 1 gm orally 3 to 4 times a day; Foals: 2 gm orally twice a day.
   b. Misoprostol: It is a synthetic analogue of $PGE_1$ exerts cytoprotective effect on gastric mucosa by preventing gastric acid secretion by inhibiting histamine-induced activation of adenyl cyclase. It also enahances bicarbonate and mucus secretion in stomach. Commonly used to prevent NSAID-induced gastric bleeding/ulceration in dogs (2.5-5 µg/kg orally three to four times a day). It is contraindicated in pregnant bitches (abortion).

D. **Inhibition of Proton Pump ($H^+K^+$-- ATPase)**: The pump operating on gastric luminal surface of parietal cells increases $H^+$ secretion into stomach in exchange of $K^+$. Inhibition of the pump causes failure of $H^+$ secretion and formation of acid in stomach.
Esmoprazole, Lansoprazole, Omeprazole: Dog: 1 mg/kg/day orally; Horse: 2-5 mg/kg/day orally.

## 11. Prokinetics

Are drugs that promote downward movement of ingesta through the GIT, by inducing coordinated GI motility (oesophageal, gastric, pyloric and duodenum). These drugs are used in gastric stasis, reflux oesophagitis and gastritis.

**Classification:** Based on mode of action:

A. **Dopamine Antagonists:** Act by antagonising the inhibitory effect of dopamine on GI motility.
Metoclopramide: Increase GI motility by central dopamine antagonism and by peripherally increasing ACh release from cholinergic neurons in GIT. It accelerates gastric emptying by increasing tone of lower oesophageal sphincter, increasing gastric contractions simultaneously pylorus and duodenum. It exerts through dopamine antagonism in CTZ.
Metoclopramide: Dog and Cat: 0.2-0.5 mg/kg, orally or SC three times a day.
Domperidone: It is a peripheral dopamine antagonist. Dog and Cat: 0.1-0.5 mg/kg IM or 0.5-1 mg/kg orally.

B. **Increasing ACh release** from parasympathetic nerve endings in myenteric plexuses in intestines and promoting intestinal motliity:
Cisapride: It is chemically related to metoclopramide, but does not possess antidopaminergic activity, Better than metoclopramide, as it increases motility of colon also in addition to that of small intestine, stomach and oesophagus. Useful in treating chronic constipation/fecal impaction in cats (usually given along with lactulose, a fecal softener). It also antagonizes 5-HT inhibition of myenteric plexuses causing enhanced intestinal motility.

C. **By preventing inactivation of ACh:** Reversible inhibitors of AChE which cause accumulation of ACh, which stimulates motility of GIT (see Cholinergic Drugs):
**Neostigmine:** Recommended for use in paralytic ileus in large animals (0.01-0.02 mg/kg SC).

## 12. Antizymotics

Are agents used to arrest or control excess intestinal fermentation and production of gas in GIT. These agents are used to relieve frothy bloat or primary ruminal tympany in ruminants and flatulent colic in horses. The antizymotics are:
Emulsion of vegetable oils (linseed, ground nut, sunflower or soybean oils): Cattle: 60-300 ml; Sheep: 100-200 ml by oral drenching.
Turpentine oil: Cattle: 15-60 ml; Sheep: 10 ml by drenching.
Poloxalene drench @ 25-40 gm in about 50 ml in cattle.
Liquor Formaldehyde drench @ 20 ml in cattle.
Phenol liquid drench @ 4 ml in horse.

## 13. Antidiarrhoeals

These are drugs used to control diarrhoea, especially acute diarrhoea. The agents are of two categories:

A. **GI Mucosal Protectants/Adsorbents**: These are not absorbed from the GIT. Reduce to irritation of intestinal mucosa caused by bacterial toxins and other nonspecific toxicants by adsorption:
Kaolin-Pectin formulation @ 1-2 ml/kg orally 3 to 4 times in a day. Kaolin is aluminum silicate and pectin is the carbohydrate obtained from the rind of *Citrus* fruits
Activated Charcoal (pore size 10-20 Å units) @ 2-10 gm/kg orally.
Bismuth subsalicylate @ 1-2 ml/kg/day in divided doses orally

B. **GI Motility Inhibitors**:
Anticholinergics: Intestinal spasmolytics: Atropine is not commonly used due to other antimuscarinic and CNS effects (excitement). Aminopentamide (0.1-0.5 mg IM, SC or orally twice a day), isopropamide (0.25-1 mg/kg orally 2 or 3 imes a day) or propantheline (0.2-0.5 mg/kg orally 2 or 3 times a day can be used (no CNS excitation).
Opiates: Produce intense constipating and anti secretary effects (mainly used as analgesics).Synthetic opioids (Diphenoxylate @ 0.05-0.1 mg/kg orally 3 or 4 times a day or loperamide @ 0.05-0.1 mg/kg orally 3 or 4 times day) having specific constipating action on intestines without significant effects on other systems. These are used in inflammatory bowel disease, but not in diarrhoea due to infections (increase in absorption of toxins) and are contraindicated in cats (CNS excitation and toxicity).

Diarrhoea due to microbial enteritis needs to be attended by administering suitable antimicrobial drugs. NSAIDs due to their antagonism of formation of prostaglandins increase intestinal secretions may also be useful in treating septicaemia or endotoxaemia.

लैक्सटिव्ह - Causing the bowles to empty.

## 14. Purgatives (डैफिकेट) - To empty the bowels. मलविसर्जन करने

Are drugs that promote defecation. Laxatives are drugs that cause mild purgation i.e. laxation, usually by a small dose of a purgative. Catharatics are agents that cause severe or drastic purgation i.e. catharasis or super purgation, usually by a large dose of a purgative. कथार्सिस

The **indications** of purgative therapy include:

A. To relieve constipation.
B. To promote elimination of ingested toxicants from the GIT.

C. To prevent straining while defecating in animals approaching parturition or in cases of prolapse of rectum or uterus.
D. To empty the intestinal contents before gastrointestinal surgery.

The use of purgatives is **contraindicated** in Advanced pregnancy (especially at high doses) to avoid incidence of abortion. Obstruction in the GIT to avoid rupture of intestines. C. Lactating animals nursing an offspring (may cause purgation in the young one).

**Classification of Purgatives**: Based on mode of action:

A. Bulk forming Purgatives. B. Osmotic or Saline Purgatives
C. Irritant or Stimulating Purgatives D. Lubricant/Emollient Purgatives
E. Neuromuscular Purgatives

A. **Bulk forming Purgatives**: Hydrophilic colloids and fibre foods. These are not absorbed in the GIT and imbibe water and swell, increasing in mass, causing distension of intestines which reflexly stimulates peristaltic activity. Celluloses and hemicelluloses present in fibre are digested by bacterial fermentation in colon, liberating hygroscopic volatile fatty acids exerting osmotic action cause bulkiness of ingesta. Increased peristaltic activity promotes easy defecation. These are given with plenty of water.

a. Methyl cellulose or carboxy methyl cellulose: Dog: 1-5 gm; Cat: 0.5-1 gm.
b. Agar agar: Dog: up to 10 gm.
c. Agar, acacia, wheat bran or rice bran with water (in large animals).
d. Pumpkin (seeds0.

B. **Osmotic or Saline Purgatives**: Inorganic salts which are poorly absorbed from GIT and are ionized in intestines are used as saline purgatives. They exert osmotic action in intestines causing retention of fluid and further drew fluid into the lumen of intestines. Increased fluid volume stimulates the peristaltic activity. Magnesium sulfate also causes secretion of cholecystokin (stimulates secretion and motility of intestines). Animals on saline purgatives should have free access to drinking water (to overcome dehydration).

a. Magnesium sulfate (Epsom salt): Commonly used in ruminants. Horse: 50-100 gm; Cattle: 250-400 gm; Foal and Calf: 25-50 gm; Sheep, Goat and Swine: 25-125 gm; Dog: 5-25 gm; Cat: 2-5 gm orally.
b. Magnesium hydroxide (Milk of magnesia): Dog and Cat: 2-10 ml; Horse: 2-3 liters orally
c. Sodium sulfate: Same as magnesium sulfate.
d. Magnesium oxide: Foal and Calf: 2-10 gm; Dog: 0.5-2 gm orally.
e. Sugar alcohols (Mannitol and sorbital) and lactulose (synthetic saccharide of fructose and lactose) are not absorbed, but undergo fermentation in large intestine with the formation of acetic, lactic and other organic acids. which also exert osmotic effect and act as osmotic purgatives.
Lactulose: Dog: 5-10 gm orally three times a day.

C. **Irritant or Stimulating Purgatives**: They increase the secretions and motor activity of the intestines through either a direct action or indirectly by activating the intramural nerve plexuses. Increased secretions and passage of water and electrolytes into intestines promote fluidity and volume enhancing peristalsis and cause purgation. Widening of pores in the epithelium/mucosal cells, making the junctions leaky through increased formation of cAMP and prostaglandins in the intestinal wall contribute the above actions.

**Classification**: Based on chemical nature of active principles:

a. Anthraquinone or emodin purgatives. b. Irritant oil purgatives.
c. Diphenylmethane derivatives.

**Anthraquinone (Emodin) Purgatives**: These are glycoside derivatives of 1,8-dihydroxyanthraquinone present in senna, cascara, rhubarb and aloes. After oral administration, the glycosides are hydrolysed by colonic bacteria liberating free aglycones called emodins. which increase peristalsis by stimulating Auerbach's plexuses. The purgative action is delayed because of time taken by the emodins to reach colon (6-12 hr in monogastrics and 12-36 hr in ruminants). After absorption active emodins to some extent are excreted through bile and milk (also purge suckling young ones). The emodin purgatives are of natural and synthetic origin.

**Natural Emodins**:

a) Casacra sagrada: Bark of *Rhamnus purshiana* (Dog: Liquid extract 2-4 ml or dry extract 0.1-0.5 ml orally)
b) Senna: Leaflets of *Cassia acutifolia* or *C. augustifolia* (Leaf powder: Horse and Cattle: 12 gm; Dog: 2-8 gm orally).
c) Rhubarb: Rhizome of *Rheum palmatum* (Powder of rhizome: Foal/Calf: 8-16 gm; Dog: 0.5-4 gm orally.
d) Aloes: It is the residue left after evaporating the fluid from the cut succulent leaves of the *Aloe* plants: *Aloe vera, A. chinensis, A. perryi* etc. (Horse: 15-30 gm; Cattle: 40-60 gm; Dog: 0.5-2 gm orally.

Synthetic Emodins: Purgative action also results only after reaching colon.
Danthron (1,8-dihydroxyanthraquinone): Horse: 15-45 gm; Cattle: 20-40 gm; Sheep: 2-5 gm/50 kg; Dog: 200-400 mg; Cat: 100-200 mg orally.

**Irritant Oil Purgatives**: Vegetable oils get hydrolysed by pancreatic lipase in small intestine into fatty acids, which undergo saponification with bile salts to form irritant soap which exerts irritant action on intestines and cause purgation.

Castor oil: Highly potent in action, capable of causing even drastic purgation. It is obtained from the dried seeds of castor bean plant *Ricinus communis*. The seeds contain 56% oil – castor oil and 26% proteins. The protein constitutes the phytotoxin ricins (See in Plant Toxicology). After oral administration the oil is hydrolysed by pancreatic lipase to glycerol and ricinoleic acid, which is saponified by salts to form sodium ricinoleate which acts as an irritant to the intestines in stimulating peristalsis. It also increases water secretion into small intestines. Similarly raw linseed oil exerts purgation through linoleates, but is less irritating than ricinoleate (linseed oil acts as a laxative). Castor oil is used in nonruminants.

Castor oil: Dog: 5-20 ml; Foals: 20-40 ml orally.

Diphenylmethane Derivatives: Induce purgation after reaching colon (delayed action). Act by irritating and stimulating intestinal motility.

Phenolphthaline: Swine: 1-2 gm; Dog: 0.02-2 gm; Cat: 15-50 mg orally. Bisacodyl: Dogs: 5-20 mg; Cats: 2.5-5 mg orally.

D. **Lubricant/Emollient Purgatives**: Mineral oil (liquid paraffin) is the most commonly used lubricant purgative. It softens and lubricates the fecal mass for easy evacuation. Its action is by prevention of water absorption in intestines. It is usually preferred in large animals with prolapse of rectum, uterus or vagina and in post-operative cases (GI surgery), in advanced pregnancy and when a segment of intestines is narrowed, where straining is not desirable. Chronic use of mineral oil results in deficiency of fat soluble vitamins (prevents absorption). It may also cause the problem of 'anal leakage' in pet dogs.
Horse and Cattle: 0.5-1 L; Foal and Calf: 50-100 ml; Dog: 5-15 ml; Cat: 2-5 ml orally.

E. **Neuromuscular Purgatives**: These include parasympathomimetics (muscarinic agonists, see Cholinergic Dugs), which cause purgation by increasing the tone and motility of intestines. Other potent pharmacological effects limit their purgative use.

Arecoline: Horse: 100-150 mg; Cattle: 10-30 mg IM; Carbachol: Horse and Cattle: 2-5 mg; Foal: 0.5-1 mg; Swine: 0.5-2 mg; Sheep: 0.25-0.5 mg SC; Physostigmine: Cattle: 30-45 mg SC; Neostigmine: Cattle: 0.01-0.02 mg/kg SC; and bethanechol. High doses produce signs of acute antiChE toxicity (accumulation of Ach; see Toxicity of Agrochemicals).

E. **Drastic Purgatives (Catharatics)**: Superpurgatives: Not used clinically.Croton oil obtained from the seeds of *Croton tiglium* and oil from the seeds of *Jatropha curcas* (Chhattisgarh fame 'biodiesel' plant). Ingestion of 1 or 2 seeds of these plants causes violent purgation in children. The seeds are famous as 'Jamalgota' in Hindi or local languages. Jalap, Colocynth, Podophyllum (vegetable origin) and barium chloride also cause drastic purgation.

**Fecal Softeners**: These soften the hard fecal masses facilitating easy propulsion in the intestines. The surfactants (docusate sodium/calcum/potassium) decrease surface tension and permit water accumulation in the fecal mass. Docusate through inhibition of cAMP in colonic mucosal cells increases fluid secretion. The docusates are used @ 2mg/kg/day orally in dog and cat; @ 10-15 mg/kg in 1.5-2 litres water orally on alternate days.

## 15. Pharmacological Considerations of Rumen

Pharmacokinetics of many of the orally administered drugs is distinctly different between monogastrics and ruminants. This is due to anatomical/functional differences between the species (simple stomach and rumino-reticulum). The examples are

a) Chloramphenicol, trimethoprim, cardiac (digitalis) glycosides etc are inactivated in anaerobic rumino-reticulum.
b) Ruminal metabolism increases the toxicity of toxicants (liberation of cyanide from cyanogenic glycosides, reduction of nitrite to nitrate etc) or decreases the toxicity of certain other toxicants (parathion to aminoparathion, inactivation of gossypol, destruction of oxalates etc).
c) Large volume of rumino-reticular contents (about 100 liters in an adult) dilutes or inactivates the drugs and reduce their absorption. While determining the drug dosage in ruminants the weight of voluminous ruminio-reticulum (about 20% in an adult) must be considered.
d) Rumino-reticular pH also significantly affects drug absorption (weak bases remain ionized and weak acids remain unionized).
e) On ruminal microflora drugs exert beneficial (antibiotics in bloat and ruminal acidosis; chloral hydrate in acetonaemia) and harmful effects (oral administration of broad spectrum antibiotics and anti-protozoan drugs disrupts the microflora suppresses bacterial fermentation and production of volatile fatty acids increasing acetic acid: propionic acid ratio, and interfere with synthesis of vitamins).

**Reticular Groove:** Efficacy of orally administered drugs in ruminants is greatly lowered due to their entry in rumino-reticulum. Closure of reticular groove with simultaneous relaxation of omasal sulcus permits entry of swallowed drug solutions directly into abomasum, bypassing rumino-reticulum. Reflex closure of reticular groove is produced by chemical irritation of pharyngeal region by administering 5-10% solution of copper sulfate, zinc sulfate, sodium bicarbonate or sodium sulfate in cattle and 1-2% copper sulfate in sheep.

## 16. Rumino-Reticular Pharmacotherapeutics

| Condition | Therapeutic Approach |
|---|---|
| Obstruction in Oesophagus | Spasmolytics: Acepromazine @ 1mg/kg IM or xylazine @ 0.05 mg/kg IM |
| Frothy Bloat | Antifoaming Agents: Emulsions of mineral or vegetable oils @ 50 ml in cattle; 150 ml in sheep. Turpentile oil @ 20-50 ml in cattle; 10 ml in sheep in with a demulcent. |
| Ruminal Impaction | Mineral oil @ 1-2 ml or dioctyl sodium sulfosuccinate @ 100 ml in 1.5 liters of water. |
| Lactic Acidosis | Antacids: Magnesium hydroxide @ 100-250 gm in Cattle; 15-25 gm in sheep or magnesium carbonate @ 20-60 gm in Cattle; 2-5 gm in sheep in about 5-10 liters of warm water |
| Simple Indigestion | Acidifying Agents: Acetic acid (4.5%) or vinegar @ about 5 liters in Cattle and 350 ml in Sheep. |
| Ruminal Atony | Cholinergic Agents: Neostigmine @ 0.01-0.02 mg/kg SC. Metoclopramide may also be used (see prokinetics) |

## EXERCISE

1. Give the classification of purgatives. Discuss the pharmacology of stimulating purgatives.
2. **Write a short note on the following:**
   a) Stomachics
   b) Emetics
   c) Antiemmetics
   d) Antacids
   e) Antiulcer drugs
   f) Prokinetics
   g) Antidiarrhoeals
   h) Emodin purgatives
   i) Irritant oil purgatives
   j) Drug disposition in rumen
   k) Reticular groove
3. **Differentiate between the following:**
   a) Sialic and antisialic
   b) Reflex emetic and central emetic
   c) Cholagougue and choleritic
   d) Intestinal astringent and intestinal demulcent
   e) Misoprostol and sucralfate
   f) Omeprazole and cimetidine/ranitidine
   g) Apomorphine and emetine
   h) Systemc and nonsystemic antacids
   i) Laxative and catharatic
   j) Methyl cellulose and magnesium sulfate
   k) Castor oil and mineral oil
   l) Central emetic and local emetic
   m) Irritant oil purgative and Lubricant purgative
   n) Neuromuscular and bulk forming purgatives
   o) Fecal softener
   p) Na+/K+ Pump and $H^+/K^+$ pump
4. **Describe the mechanism of action of the following:**
   a) Apomorphine
   b) Metoclopramide
   c) Sucralfate
   d) Misoprostol
   e) Omeprazole
   f) Osmotic purgative
   g) Anthraquinone
   h) Castor oil
   i) Emodin
   j) Cisapride
   k) Castor oil
5. **Define the following and give one example for each:**
   a) Sialagogue
   b) Antisialic
   c) Bitter stomachic
   d) Carminative
   e) Emetic
   f) Antiemetic
   g) Cholagogue
   h) Choleritic
   i) Lipotropic
   j) Intestinal astringent
   k) Intestinal demulcent
   l) Appetizer
   m) Anorectic
   n) Antacid
   o) Prokinetic
   p) Antizymotic
   q) Purgative
   r) Laxative
   s) Catharatic
6. **What do you mean by the following? Answer in one or two sentences for each:**
   a) Reticular groove
   b) CTZ
   c) Cholesystokinin
   d) Achlorhydria
   e) Betazole
   f) Adsorbent
   g) Mucosal protectant
   h) $H^+/K^+$ pump
   i) *Helicobacter*
   j) Mineral oil
   k) Nuxvomica
   l) Cholekinetic
   m) Gastric sedative
7. **Give the clinical uses of the following drugs:**
   a) Purgatives
   b) Emetics
   c) Prokinetics
   d) Antacids
   e) Anticmetics
   f) Stomachics
8. **Give the dose and route of administration of the following drugs:**
   a) Apomorphine in dog
   b) Prochloperazine in dog
   c) Diphenhydramine in dog
   d) Mg hydroxide in cattle
   e) Mg carbonate in buffaloes
   f) Famotidine in horse
   g) Cimetidine in dog
   h) Sucralfate in foal
   i) Misoprostol in dog
   j) Metoclopramide in dog
   k) Turpentine oil in cattle/sheep
   l) Mg sulfate in Cattle/Goat
   m) Senna in horse/cttle
   n) Danthron in dog/cat
   o) Castor oil in dog/foal
   p) Bisacodyl in cat/dog
9. **Suggest the drug of choice for the following, give its dose and route of administration:**
   a) Xerostomia in a dog
   b) Gastric ulcer in a dog/foal
   c) Colic in a horse
   d) Ruminal atony in a cow/buffalo
   e) Bloat in a cow
   f) Appetizer in a sheep/cow/dog
   g) Emesis in a dog
   h) Purgative in a dog/cat/horse/cow/goat
   i) Anorectic in a dog/cat
   j) Oesophageal obstruction in a cow
   k) Frothy bloat in a buffalo
   l) Ruminal impaction in a cow
   m) Lactic acidosis in a sheep
   n) Simple indigestion in cattle
   o) Paralytic ileus in a horse
   p) Chronic fecal impaction in a cat
   q) Flatulent colic in a horse
   r) Constipation in advanced pregnant cow
   s) Purgation in a cow with uterine prolapse
   t) Constpation in GI postoperative cow
   u) To remove ingested rat bait in dog
   v) To remove ingested pesticide in a cow

10. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
    a) Simple bitter: Gentian/Quassia
    b) Alkaloidal bitter: Nuxvomica
    c) Nauseating/Emetic bitter: Ipecacuanha
    d) Sialagogue: Arecoline/Physostigmine
    e) Antisiaclic: Atropine/Glycopyrrolate
    f) Xerostomia: Sialagogue
    g) Preanaesthetic: Antisialic
    h) Stomachic: Nuxvomica/Ginger/Gentian
    i) Central emetic: Apomorphine/Xylazine
    j) Reflex emetic: Na salts/CuSO4/H2O2
    k) Mixed emetic: Ipecac/Emetine
    l) Neostigmine: AntiChE prokinetic
    m) Metoclopramide: Antidopaminergic prokinetic
    n) Antiemetic: Isopropamide/Propatheline/Acepromazine/Prochlorperazine/Mecline/Cyclizine/Ondasteron/ Diphenhydramine/ Metoclopromaide/ Butorphanol
    o) Intestinal astringent: Tannic acid/Catechu/Ammonium hydroxide gel
    p) Intestinal adsorbent: Used in diarrhea/Kaolin/Bismuth carbonate
    q) Appetizer: Prednisone/Stanozolol/Cyproheptadine/Diazepam/Oxazepam
    r) Anorectic: Antiappetizer/Amphetamine/Fenfluramine/Fluoxetine/Sibutramine
    s) Antacid: Mg hydroxide/Mg carbonate/Al hydroxide/Mg oxide/Ca carbonate
    t) Antiulcer drug: Anacids/Cimetidine/Ranitidine/Famotedine/Sucralfate/Misoprostol/Omeprazoloe
    u) Cytoprotective on gastric mucosa: Sucralfate/Misoprostol/Omeprazole
    v) Sucralfate: Protective coat over ulcerated gastric mucosa/Prevents back diffusion of $H^+$/Promotes formation and release of $PGE_1$
    w) Misoprostol: Prevents gastric acid secretion/Inhibits activation of gastric mucosal adenyl cyclase/ Increases bicarbonate secretion/Increases mucus secretion
    x) Omeprazole: Inhibition of $Na^+/K^+$ pump/Failure of secretion of $H^+$ secretion
    y) Prokinetic: Metoclopramide/Domperidone/Cisapride/Neostigmine
    a) Cisapride: Nondopaminergic prokinetic/ Promotes release of Ach/Atagonizes 5-HT
    b) Antizymotic: Tupentine oil/Poloxalene/Liquor formaldehyde/Liquid phenol
    c) GI mucosal adsorbent: Kaolin-pectin/Activated charcoal/Bismuth subsalicylate
    d) GI mucosal motility inhibitor: Atropine/Isopropamide/Propantheline/Diphenoxylate/Aminopentamide
    e) Diphenoxylate/Loperamide: Synthetic opioid
    f) Irritant oil purgative: Castor oil
    g) Lubricant oil purgative: Liquid paraffin
    h) Neuromuscular purgative: Arecoline
    i) Drastic purgative Croton oil
    j) Fecal softener: Docusate
    k) Frothy bloat: Turpentine oil
    l) Ruminal impaction: Mineral oil
    m) Synthetic emodin: Danthrone
    n) Natural emodin: Senna/Cascara/Aloes/ Rhubarb
    o) Lactic acidosis: Mg hydroxide/Mg carbonate
    p) Ruminal atony: Neostigmine/ Metoclopramide
    q) Reticular groove: $CuSO_4$/$ZnSO_4$/Sodium bicarbonate/Sodium sulfate
    r) Bulk purgative: Methyl cellulose/Agar agar/Wheat bran/Pumpkin/Rice bran
    s) Osmotic purgative: Mg sulfate/Mg hydroxide/Na sulfate/Mg oxide/Mannitol/Sorbital/Lactulose
    t) Irritant purgative: Anthraquinone/Emodin/Castor oil/Phenolphthaline/Cascara sagrada/Senna/Rhubarb

11. **Give the source of the following**:
    a) Gentian
    b) Nuxvomica
    c) Arecoline
    d) Physostigmine
    e) Ginger
    f) Turpentine oil
    g) Eucalyptus oil
    h) Emetine
    i) Podophyllum
    j) Catechu
    k) Pectin
    l) Atropine
    m) Castor oil
    n) Croton oil
    o) Cascara sagrada
    p) Agar agar
    q) Senna
    r) Rhubarb
    s) Aloes

12. **Give the most appropriate reason for each of the following statements**:
    a) Atropine/glycopyrrolate is used as preanaesthetic.
    b) Apomorphine causes emesis.
    c) Sodium salts cause emesis.
    d) Isopropamide/Prapantheline is an antiemetic.
    e) Acepromazine/Prochlorperazine is an antiemetic.
    f) *Croton* oil or *Jatropha* oil is not a clinical purgative.
    g) Bitters promote digestion of food.
    h) Turpentine oil is used in flatulence.
    i) Emetine is a mixed action emetic.
    j) Cyproheptadine acts as an appetizer.
    k) Benzodiazepines promote appetite.
    l) Amphetamine is an anorectic
    m) $H_2$ antagonists exert antiulcer action.

n) Antihistamines also act as central antiemetics.
o) Metoclopramide is mixed acting antiemetic.
p) Ondasteron/Dolasetron is a mixed acting antiemetic.
q) Kaolin-pectin formulation is used in diarrhea.
r) Omeprazole is used as an antiulcer drug in dogs.
s) Fibre foods/Celluloses act as bulk purgatives.
t) Mangesium salts act as saline purgatives.
u) Emodin/Phenolphthaline purgation is delayed.
v) Diphenoxylate/Loperamide is used in diarrhea.
w) Sodium bicarbonate produces acid rebound action.
x) Sucralfate/Misoprostol exerts cyotoprotective action on gastric mucosa.
y) Fluoxetine/Fenfluramine/Sibutramine suppresses appetite.
z) Antacids exert gastric mucosal protection in hyperacidity.
a) Long term NSAID therapy is to be supplemented with misoprostol treatment.
b) Cisapride is chemically related. but not in its prokinetic action to metoclopramide.
c) Cisapride is used along with lactulose in treating chronic constipation/fecal impaction in cats.
d) Diarrhoea due to microbial enteritis is to be treated by giving a suitable antibiotic coupled with a NSAID.
e) Senna/Rhubarb/Cascara/Aloes/Danthron acts as stimulating purgatives.
f) Mineral oil is the most commonly used purgative in animals.
g) Mineral oil is used to relieve constipation in case of prolapse of rectum. uterus or vagina. post operative GI surgery. advanced pregnancy and when segment of intestines is narrowed.
h) Chronic use of mineral oil causes night blind ness or in young animals rickets.
i) Chronic use of mineral oil in pet dogs may be problematic.
j) GI disposition of drugs in a ruminat is different from that of a monogastric.
k) Closure of reticular groove helps in increasing the efficacy of orally administered drugs in ruminants.
l) Neostigmine/Metoclopramde is used to treat ruminal atony.
m) Bitters can be used as sialics as well as stomachics.

# Chapter – 23: DRUGS ACTING ON CARDIOVASCULAR SYSTEM

## 1. Cardiotonics

These are drugs, which specifically increase the force of contraction (positive ionotropic action) of failing heart. Increase the functional capacity of cardiac muscle without corresponding increase in oxygen consumption of myocardium. Used in treating CHF, oedema of cardiac orgin and cardiac asthma.

**Cardiac Glycosides**: Are of plant origin:

| Name of the Plant | Part of the Plant | Name of Glycoside |
|---|---|---|
| *Digitalis lanata* | Leaves | Digitoxin, gitoxin and digoxin |
| *Digitalis purpurea* | Leaves | Digitoxin, gitoxin and gitalin |
| *Strophanthus gratus* | Seeds | Strophanthin G (Ouabain) |
| *Urgenia maritime* | Bulb | Proscillaridin A |

The glycosides consist of two parts: A sugar and a nonugar called aglycone or genin; pharmacological activity resides in the aglycone: Digitoxigenin, gitoxigenin, digoxigenin etc. The sugar moiety determines the solubility and cell permeability of the aglycone.

**Pharmacological Effects of Cardiac Glycosides**: The major effect is on heart

A. Heart Rate: Decrease in heart rate (negative chronotropic action) through reflex vagal stimulation and direct vagal centre stimulation.
B. Cardiac Tone: Dose-dependent increase in tone/force of contraction of heart (strong ionotropic action).
C. Conductivity: Increase in conductivity and decrease in refractory period in atrial and ventricular muscles.
D. Automaticity: Increased in all areas of heart, except the SA node.
E. Coronory Blood Vessels: Blood flow moderately increased due to increased cardiac out put.
F. Cardiac Out Put: Increased.
G. Heart Size: Markedly reduced.
H. Other Effects: Diuresis in CHF due to increased GFR (increased renal blood flow) and reduction in oedema. No effect on CNS in therapeutic doses, but vomiting at high doses through stimulation of CTZ.

The saluatory effect of cardiac glycosides is strong positive ionotropic action accompanied by negative chronotropic effect, which is more pronounced in failing heart (CHF). The sequence of effects in relieving CHF is as follows:

Increase in force of contraction → Decrease in heart rate → Reduction in end diastolic pressure → Increase in cardiac out put → Reduction in sympathetic tone → Decrease in blood volume → Reduction in venous pooling → Increase in renal blood flow → Diuresis and relief of oedema → Reduction in heart size.

**Mechanism of Positive Ionotropic Action:** Inhibition of $Na^+/K^+$-ATPase pump. The enzyme is located on the myocardial cell membrane. Following its inhibition $Na^+$ concentration increases within the myocardial cell promoting $Ca^{++}$ exchange into the cell, causing availability of more $Ca^{++}$ in myocardial muscle cell to interact with contractile proteins (activation of troponin-tropomyosin) resulting in increased contractility i.e. increased force of contraction of myocardium as a whole. Digitalis glycosides also potentiate cardiac vagal activity.

The renin-angiotensin system also has a role in the genesis of CHF, where renin release promotes formation of angiotensin II by the action of angiotensin converting enzyme (ACE) which in turn leads to increase in aldosterone secretion and $Na^+$ retention. Angiotensin II also increases vascular resistance and BP. Therefore, use of ACE inhibitors with cardiac glycosides cause decreased $Na^+$ retention, increased diuresis, decreased vascular resistance and venous pressure and increased cardiac out put.

**Digitalization**: Procedure followed for administration of cardiac glycosides in treatment of CHF. It consists of administration of an initial large non-toxic dose to produce an observable therapeutic action called 'loading dose' or digitalization dose, which is followed by administration of small divided doses to sustain the desired effect over a period of time (2-3 days) called 'maintenance dose'. Digitalization may be of three types:

A. **Slow Digitalization**: Preferred in mild cases of CHF. Consists of administration of 1/5$^{th}$ of the total calculated dose at 10 hr intervals within two days in mild cases
B. **Rapid Digitalization**: Preferred in moderately severe cases of CHF to achieve rapid clinical response. The total dose is divided into three equal parts and administered at 6-hour intervals.
C. **Intense Digitalization**: This method is preferred in very severe cases as an emergency treatment. Half of the total calculated dose is administered at once, followed by 1/4$^{th}$ of the dose after 6 hr and continuation of 1/8$^{th}$ the dose at 4-6 hr intervals until the desired therapeutic effect is evident.

**Signs of Digitalization**: Digitalization must be followed with ECG monitoring. The signs include:
A. Relief from coughing.
B. Relief in respiratory distress.
C. Diuresis.
D. Reduction in body weight.
E. Improved ECG changes: Increase in PR-interval, decrease in QT-interval, deviation of ST-segment, change in direction of T-wave and flattening of P-wave.

**Toxic Signs of Excessive Digitalization (Digitalis toxicity)**: Anorexia, nausea, dyspnoea, palpitation, cardiac arrhythmia (complete/partial heart block: premature contraction or tachycardia) and necrosis of myocardium.

**Interaction with Other Drugs**: Quinidine displaces digoxin from plasma protein binding and increases digoxin level in blood. Diuretics with cardiac glycosides promote hypokalemia. Glucocorticoids also potentiate digitalis-induced hypokalemia.

**Clinical Uses of Cardiac Glycosides**:
1. Treatment of CHF (along with diuretics and ACE inhibitors/vasodilators).
2. Treatment of myocarditis.
3. In cardiac arrhythmia ( atrial flutter/fibrillation and paroxysmal supraventricular tachycardia)

**Digitalization Doses in Animals**:

| Animal | Route | Glycoside | Loading Dose (mg/kg) | Maintenance Dose (mg/kg/day) |
|---|---|---|---|---|
| Dog | Oral | Digoxin<br>Digitoxin | 0.11 – 0.22<br>0.022 – 0.044 | 0.011 at 12 hr interval<br>0.0022 – 0.0044 |
| | Parenteral | Digoxin<br>Ouabain | 0.022 – 0.044<br>0.022 – 0.044 | 0.011 at 12 hr interval orally<br>0.011 at 12 hr intervals |
| Horse | Oral | Digitoxin<br>Digoxin | Total Dose : 0.033 – 0.066<br>Total Dose : 0.066 | |
| | Parenteral | Digoxin<br>Ouabain | Total Dose : 0.022 – 0.0.33<br>Total Dose : 0.013 – 0.22 | |
| Cattle | Parenteral | Digitoxin<br>Digoxin<br>Ouabain | Total Dose : 0.03<br>Total Dose : 0.0088<br>Total Dose : 0.01 – 0.02 | |

Use of ACE inhibitor enalapril alone @ 0.5 mg/kg twice a day orally or in conjunction with digoxin and furosemide@ 0.5 mg/kg/day orally is recommended in treating CHF in dogs. Benazepril another ACE inhibitor can also be used (Dog and Cat: 0.25-0.5 mg/kg/day orally).

## 2. Cardiac Stimulants

Are drugs used to stimulate the failing heart (acute heart failure) exerting both positive ionotropic as well as chronotropic action.

**Classification**: Based on mechanism of action:

**A. By Increasing Sympathetic Activity**: **Sympathomimetics**: Have stimulant on myocardium, both positive ionotropic and chronotropic effects.

**Epinephrine** (Adrenaline hydrochloride): 1:1,000 dilution @ 0.1-0.3 ml IV or SC in dog and 2-4 ml in horse; in 1:10,000 dilution @ 0.5-1 ml by intracardiac injection into left ventricle.

**β-Adrenoceptor Agonists:** Through activation of myocardial cell $\beta_1$-adrenoceptors (G-protein coupled receptors) stimulate adenyl cyclase and increase cAMP production causing subsequent transduction mechanisms in increasing force of contraction of myocardium:

**Dopamine** with $\beta_1$ activation has positive ionotropic effect and with activation of $\beta_2$ receptors in renal tubules dopaminergic receptors increases renal blood flow and diuresis (Dog: 2-12 µg/kg/min IV infusion).

**Dobutamine**, a synthetic dopamine analogue has more effective positive ionotropic effect and less chronotropic effect than dopamine (Cat and Dog: 0.5-15 µg/kg/min IV infusion as per the need)

**Isoproterinol** (isoprenaline) @ 3.5 microgram/kg by slow IV injection.

**B. By Decreasing Parasympathetic Activity by Parasympatholytics**: Increase heart rate by antagonizing parasympathetic control over the heart (by blocking cardiac muscarinic receptors: Atropine and hyoscine. Not clinically used due to their other anti-muscarinic effects.

**C. By Decreasing Breakdown of cAMP**: **Xanthine Derivatives**: **Phosphodiesterase Inhibitors**: These drugs increase myocardial intracellular cAMP levels and increase myocardial contractions by inhibiting phosphodiesterase (PDE) which breaks cAMP. Increase inward current of $Ca^{++}$ into myocardial cells and also promote their release from intracellular stores (intracardiac sarcoplasmic reticulum).

**Methylxanthine Derivatives**: Theophylline, aminophylline and caffeine. Aminophylline is used in treatment of pulmonary emphysema in horses (2.5 gm orally for 2-3 days) and cardiac asthma in dogs (5-100 mg orally). These drugs also stimulate medullary vasomotor centre.

**Bipyridine Derivatives**: Amrinone and milrinone increase myocardial contractility. Useful in treating CHF (Dog and Cat: 1-2 mg/kg in normal saline IV, followed by infusion @ 10-100 µg/kg/min as per the need). These drugs also cause peripheral vasodilatation.

**Benzimidazole-pyridazinone derivatives**: Pimobendan (Dog: 0.1-0.2 mg/kg orally twice a day).

**D. By Increasing Contractility of Cardiac Muscle**: **Calcium ions**: Directly stimulate the myocardium by increasing both force and rate of contraction, making availability of $Ca^{++}$ to interact with contractile proteins (activation of actomyosin complex). Calcium chloride solution (10%) or calcium borogluconate injection @ 2-4 ml, preceeded by 2-3 ml of potassium citrate IV as a last resort to revive the heart.

**Note**: In reversal of cardiac arrest, therapy must be instituted at once along with respiratory stimulants and cardiac massage

| **Differences between** | **Cardiotonics** | **Cardiac Stimulants** |
|---|---|---|
| 1. Action: | Positive ionotropic and Negative chronotropic | Positive ionotropic and chronotropic |
| 2. Onset of Action: | Slow | Immediate |
| 3. Duration of Action : | Prolonged | Short |
| 4. Size of Heart: | Decreased due to increase in tone | No effect on tone and size |
| 5. Oxygen Demand: | No proportionate increase | Disproportionate Increase |

| | | | |
|---|---|---|---|
| 6. | Cardiac Efficiency: | Increase | Decrease |
| 7. | Mode of Action: | Inhibition of $Na^+/K^+$ ATpase | Through specific receptors |
| 8. | Use: | Mainly in CHF | Acute heart failure |

### 3. Antiarrhythmic Drugs

These are cardiac depressant drugs (Dysrrhythmic Drugs) used in the treatment of cardiac arrhythmia (tachaarhythmia: flutter and fibrillation).

**Classification:** Basing on mode of action:

**A. Class I: Sodium Channel Blockers**: Block $Na^+$ entry into myocardial cell and prevent its depolarization (failure of initiation of MAP; stabilize myocardial muscle cell membrane like local anaesthetics in stabilizing nerve membrane) and reduce conduction rate and amplitude of electrical cycles. These drugs are sub-divided into three categories according to the state of $Na^+$ channel (resting, open or refractory) to which they bind

a. Quinidine, procainamide and disopyramide: Bind rapidly to the channel in open or refractory state (tachyarrhythmia): Use dependence: More of the activation of the channel, greater will be the channel block (ischaemic muscle).

b. Lidocaine, phenytoin and mexiletine: Bind rapidly with and dissociate from the channel during '0' phase of action potential (normal course of heart beat) and also in refractory phase when myocardial cells are depolarized (ischaemic muscle).

c. Flecainide, encainide and indecainide: Bind to and dissociate from the channels slowly irrespective of the state.

**B. Class II: $\beta_1$-Adrenoceptor Blockers**: Leads to negative ionotropic and chronotropic effects: Propranolol, acebutolol, metoprolol, nadolol, atenol, esmolol, temolol etc. These interfere with calcium ion-induced excitation of AV node

**C. Class III: By Prolonging the Duration of Action Potential**: These drugs prolong the depolarization phase of MAP and thus reduce the rate of contraction. This action is due to blocking of $K^+$ channels and outward its efflux decreasing the excitability and inhibiting the spontaneous activity. Prolonged action potential is followed by prolongation of refractory period: Amiodarone, bretylium, dofetilide, ibutilide and satolol (also a nonselective β–blocker).

**D. Class IV: Calcium Channel Blockers:** These drugs prevent entry of $Ca^{++}$ into the myocardial cells (AV node and bundle of His) and thus prevent $Ca^{++}$-induced activation of actomyosin complex and contraction of myocardium: Verapamil, diltiazim, nifedipine, amlodipine.

The antiarrhythmic drugs exert cardiac depressant activity by altering **electrophysiological properties** (EP Property) in cardiac tissues as outlined below:

| EP Property | Effect | Drug Class |
|---|---|---|
| Automaticity | Decrease | All four |
| Excitability | Decrease | All four |
| Conduction Velocity | No change or increase | All four |
| Effective Refractory Period | Increase | All four except I. b |
| | Decrease | 1. b |

**Doses and Administration of Anti-arrhythmic Drugs in Animals**

| Drug | Species | Route | Dose and Intervals |
|---|---|---|---|
| Quinidine | Dog/Cat | IM | 5-20 mg/kg at 6-8 hr intervals |
| | Horse | Oral | 20 mg/kg every two hr |
| | | IV | (Gluconate) 1-1.5 mg/kg every 5-10 min |

| | | | |
|---|---|---|---|
| Procainamide | Dog | IM<br>Oral | 8-16 mg/kg at 3-6 hr intervals<br>5-20 mg/kg/day at 4-6 hr intervals |
| Phenytoin | Dog | Oral<br>Slow IV | 5-10 mg/kg at 8 hr intervals in three divided doses<br>2-5 mg/kg once |
| Lidocaine | Dog | Slow IV | 0.5-2 mg/kg at 30-60 minute intervals |
| Propranolol | Dog | Slow IV | 0.05-0.15 mg/kg till effect |
| Tocainide | Dog | Oral | 15-30 mg/kg at 8 hr intervals |
| Mexilitine | Dog | Oral | 5-10 mg/kg at 8 hr intervals |

**Note:** Treatment should be continued under constant cardiac monitoring

**4. Antihypertensive Drugs**

Are drugs used to reduce the elevated blood pressure (especially in human hypertensive patients).

**Classification**: Based on mechanism of action:

A. **By interfering with central sympathetic activity**: Methyldopa and Clonidine (see sympatholytics)

B. **Through Peripheral Adrenoceptor Antagonism**:
   1) **Alpha-adrenergic receptor blockers**: Phentolamine, phenoxybenzamine, tolazoline etc.
   2) **Beta-adrenergic receptor blockers**: Propranolol, metoprolol, nadolol, atenolol etc.
   3) **Both alpha and beta-adrenergic receptor blockers**: Labetalol

C. **Drugs interfering with Function of Postganglionic Sympathetic Nerves**: Guanethidine, reserpine, metyrosine, carbidopa and methyldopa.

D. **By dilatation of blood vessels (Vasodilators)** S.NO 66.
   a) **Direct Acting Vasodilators:**
   1. Calcium channel blockers: Nefidipine, dilitiazem, nicardipine, felodipine, nimodipine, amlodipine, verapamil etc cause generalized vasodilation, including arterial dilatation.
   2. Potassium channel activiation: Cromakalim, minoxidil and nicorandil: Relax vascular smooth muscle by selective increase in $K^+$ permeability (hyperpolarization). Nicorandil also has NO-donor action.
   3. Increasing cyclic nucleotides: cGMP activation by NO, nitrates and natriuretic peptides. cAMP activation by $\beta_2$ agonists, adenosine, $PGI_2$ and dopamine ($\beta_2$ in renal vessels). Selective phosphodiesterase (PDE) type V inhibitors (sildenafil) inhibit breakdown of cGMP has clinical application in penile erectile dysfunction. The pelvic nitrinergic nerves release NO, which activates cGMP in smooth muscles in corpora cavernosa causing vasodilatation and increased blood flow into corpora cavernosa, causing penile erection. Sildefanil by selectively inhibiting the PDE increases cGMP levels. Penile erection occurs on sexual stimulation only, after about one hr of ingestion of the drug.

Nitroprusside (nitroferricyanide) exrerts powerfull vasodilatation by liberation of NO. Nitroprusside contains HCN. Its toxicity resembles that of CN.

Anyl nitrite, nitroglycerin, isosorbide and mononitrate: These are better known as antiangina drugs; relax vascular, oesophageal and biliary smooth muscles. Nitrite is converted to NO, which in smooth muscles of vasculature combine with thiols forming nitroso-thiols. The nitroso-thiols activate guanylate cyclase which catalyzes GTP to cGMP. cGMP inhibits calcium activation of myosin light chain kinase preventing smooth muscle contraction causing dilatation of blood vessels. Nitrites cause dilatation of coronary arteries, including the collateral arterioles, increasing blood flow to ischaemic area of cardiac muscle through coronary redistribution (dipyridamole does not increase collateral dilatation). In addition, oxygen consumption by myocardium is decreased secondary to pre-load (veno-relaxation) and after-load (dilatation of arteries). The increase in cGMP by nitrites (in antagonistic to cAMP) also exerts antithrombotic action (cAMP is necessary for platelet activation-aggregation cascade).

b) **Indirect Acting Vasodilators**: By interfering with Renin-Angiotensin System:
   1. Renin Inhibitors: Enalakiren
   2. ACE Inhibitors: Captopril, enalapril, lisinopril, ramipril, benazepril, perindopril, trandolapril etc.
   3. Angiotensin II receptor (subtype I) antagonists: Saralasin and losartan

c) **Vasodilators with Unknown Function**: Hydralazine and minoxidil cause generalized arteriolar dilatation (arterial dilators) resulting in fall in BP, reflex tachycardia and increased output.

**E. Ganglionic Blockers**: Trimethaphan, mecamylamine, pentolinium etc.

**Epoprostenol** (prostacyclin analog) antagonizes vasoconstrictor effect of thromboxanes and used in pulmonary hypertension in man.

## 5. Haematinics

These drugs promote haemoglobin synthesis and/or erythropoiesis in general and are used in the treatment of anaemia (Anti-anaemic Drugs).

A. **Iron Deficiency Anaemia**: Iron compounds are used:
   a) Ferrous Sulfate: Horse: 5-10 gm; Cattle: 10-15 gm; Sheep and Swine: 0.5-2.5 gm; Cat: 0.05-0.2 gm per day orally for 2-3 weeks.
   b) Ferrous Phosphate: In small animals: 2-4 ml/day orally for about a week
   c) Ferrous gluconate or ferrous succinate: In small animals: 0.25 gm/day orally for 3-5 days.
   d) Iron dextran injection: Piglets: 2ml containing 100 mg ferric iron IM on 2nd or 3rd day of birth, repeat 10 days after, if necessary.

B. **Copper Deficiency Anaemia**: Copper compounds are used. Copper is essential for utilization of iron:
   a) Copper sulfate: Sow: 80 mg; Cow: 200 mg IV.
   b) Copper glycinate: Sow: 45 mg; Cow: 120 mg IM
   c) Copper sulfation in food: Large animals: 2 gm/day; Small animals: 1g/day.
   A combination of ferrous and copper sulfates (5:1 ratio) is used for treatment of piglet anaemia. A mixture of 100 gm ferrous sulfate, 200 gm copper sulfate and 100 gm treacle is smeared on the teats of sow once or twice in a day. The piglets are also treated by oral doses of 5 ml solution containing 2 gm ferrous sulfate and 0.65 gm copper sulfate in 100 ml distilled water. Treatment to be continued till improvement.

D. **Cobalt Deficiency**: Cobalt is utilized by ruminal microflora for synthesis of vitamin $B_{12}$. Cobalt chloride or sulfate: Cattle: 0.2-0.5 gm; Sow: 0.05-0.1 gm/day through feed or drench.

E. **Hydroxycobalamin (Vitamin $B_{12}$) Deficiency**: It is necessary for synthesis of nucleoproteins during erythropoisis. Deficiency causes pernicious anaemia. All species: 2-5 µg/kg/day IM.

F. **Folic Acid Deficiency**: Folic acid (pteroylglutamic acid) is also essential for synthesis of RNA and DNA (multiplication of RBC). Its deficiency causes megaloblastic anaemia. Dietary contribution is the main source, but it is also synthesized by intestinal microflora. Dog and Cat: 2.5-5 mg/day orally.

**Erythropoietin** (EPO): It is a glycoprotein hormone produced by the renal peritubular cells. It is essential for normal erythropoisis. Anaemia leads to hypoxia, which is sensed by the renal peritubular cells and release/secrete EPO. The EPO then acts on bone marrow stimulating proliferation of colony forming cells of the erythroid series and induces haemoglobin formation and eryhthroblast maturation. EPO is mainly indicated in anemia due to chronic renal failure.

## 6. Blood Coagulants

These are agents which promote blood clotting and used for arresting haemorrhage (Haemostatics).

**Classification:** Based on site of action:

**A. Local Haemostatics:** Used over bleeding surfaces; help in blood clot formation and stop bleeding.

**I. Natural or Physiological Haemostatics:**

a) **Thromboplastin**: Commercial thromboplastin powder is the saline extract of cattle brain or acetone extract of rabbit lung and/or brain.

b) **Thrombin**: A white powder made from interaction of thromboplastin and calcium with bovine prothrombin. It is used in powder form or as solution (1000 units/ml) in normal saline or sterile distilled water.One unit of thrombin corresponds to the quantity of thrombin required to clot one ml of fibrinogen solution in 15 seconds.

c) **Fibrin**: It is available as fibrin foam strips. The strips soaked in thromboplastin solution when applied over bleeding surface arrest bleeding.

d) **Fibrinogen**: Made from human plasma. Available as 2% solution in normal saline.

**Note:** Though physiological, the above haemostatics should not be administered systemically (cause massive intravascular clots).

**II. Synthetic Local Haemostatics:** These are especially used to prevent post-operative bleeding during surgery.

a) Absorbable Gelatin Sponge: It is applied after soaking in thrombin solution (100 Units/ml). When left in bleeding areas (before closing the wound) the sponge is absorbed within six weeks.

b) Calcium Alginate: Absorbable haemostatic applied as fibrous calcium alginate dressing dipped in sodium alginate solution.

c) Oxidized Cellulose: It is the surgical gauze containing oxidized cellulose. When kept over bleeding surfaces stops bleeding.

d) Astringents (Ferric sulfate, silver nitrate and tannic acid): Act by precipitating proteins of bleeding surfaces and arrest bleeding. Their disadvantage is damage to the surrounding tissues.

**B. Systemic Blood Coagulants:** Used systemically to stop haemorrhages in haemorrhagic syndromes (failure of normal blood clotting mechanisms):

a) Whole Blood Transfusion: Replenishes deficient clotting factors.

b) Vitamin K: Promotes hepatic synthesis of clotting factors. Used in prophylaxis and treatment of bleeding disorders due to deficiency of clotting factors. All species: 0.25-2.5 mg/kg IM.

c) A 1:1 mixture of malonic and oxalic acids (5% solutions of each). The mixture acts through liberating clotting factors by rupturing the platelets: Large animals: 5-25 ml; Small animals: 0.5-2.5 ml IV or IM.

d) **Protamine sulfate**: Heparin antagonist. Inactivates heparin by forming a complex

e) **Epsilon aminocaproic acid and tranexamic acid** are water soluble derivatives of lysine; acts by binding to plasminogen and consequently inhibiting its activation to plasmin (antithrombolytic effect). Used in human medicine (bleeding due to thrombocytopaenia or postpartum hemorrhage).

Snake venoms (vipers) promote blood coagulation by stimulating thrombokinase.

## 7. Blood Anticoagulants

These are drugs used to prevent blood clotting.

**Classification**: Based on use *in vitro* or *in vivo*:

**A. *In Vitro* Anticoagulants**: Used to prevent clotting of blood intended for transfusion or diagnostic use.

a) 20% solution of sodium oxalate @ 0.01 m/ml of blood.

b) 25% solution of sodium citrate @ 0.01 ml/ml of blood.

c) Sodium EDTA @ 0.1 mg/ml of blood.

d) Heparin sodium @ 4-6 Units/ ml of blood.

The above solutions may be added to vials in the required quantity and evaporated to dryness before adding the blood samples.

**B. *In Vivo* Anticoagulants**: These are used systemically to prevent intravascular thrombus formation (pulmonary embolism). Two groups basing on their route of administration:

i) IV Anticoagulants: Heparin sodium: Physiological anticoagulant present in mast cells along with histamine, helps in maintaining fluid state of blood especially in minute blood vessels. Heparin is ineffective orally. Dog: 75-250 U/kg IV; Cat: 75-375 U/kg IV; Horse: 25-100 U/kg IV, 2-3 times a day in the three species). Enoxoparin is heparin of porcine origin. Danaparin is a heparinoid anticoagulant.

ii) Oral Anticoagulants: Coumarin derivatives (Warfarin, phencoumon, acenocoumarol etc) and indanedione derivatives (anisindione, pindone). Their anticoagulant effect is delayed (require time for establishing anti-vitamin K effect). Warfarin has long half-life (excessive protein binding). Bishydroxycoumarin is the cause of haemorrhagic syndrome observed in sweet clover (which contains dicoumarol) poisoning in cattle. Warfarin: Dog and Cat: 0.1-0.2 mg/kg/day orally; Horse: 0.07-0.17 mg/kg/day orally.

**Mechanisms of Blood Anticoagulant Actions:**

***In Vitro* Anticoagulants**: Cause anticoagulant effect by preventing participation of calcium ions in blood clotting mechanisms. Formation of insoluble calcium salts by citrate and oxalates, and chelation of calcium ions by disodium EDTA. Calcium ions are necessary for conversion of prothrombin to thrombin and activation of clotting factors IX and X.

***In Vivo* Anticoagulants:** Heparin acts by activating plasma antithrombin III (AT III) and preventing subsequent activation of the accelerating enzyme (serine proteases) cascade, starting with Hageman Factor (Factor XII) followed by factors XI, IX, X and finally the factor II (thrombin). Fluid state of blood is maintained by inhibiting the clotting enyme cascade. The AT III seves this purpose. Heparin (present in mast cells along with histamine) acts as physiological anticoagulant through activation of AT III. Heparin also acts as an *in vitro* anticoagulant. **Hirudin** (anticoagulant from leech), hirugen (derivative of hirudin) and argatroban (competitive inhibitor of thrombin) inactivate thrombin (antithrombin anticoagulants).

The oral anticoagulants act as vitamin K anticoagulants (Koagulation); block regeneration of reduced vitamin K (hydroquinone), an essential cofactor of carboxylase enzyme mediates γ-carboxylation of glutamic acid residue of coagulation factors II, VII, IX and X. Thus vitamin K antagonists prevent the formation of these clotting factors. Therefore, the oral anticoagulants act in a manner similar to functional vitamin K deficiency.

**Antiplatelet drugs** prevent aggregation of platelets in the genesis of thromboembolic disease. The clinically important drug is asprin, which has antiplatelet effect through reducing the synthesis of $TXA_2$ by inhibition of COX I (in platelets preventing their aggregation and also reduces vasoconstriction: promote bleeding). Indomethacin also has this action. Asprin's clinical application includes acute myocardial infarction, after coronary bypass surgery and coronary angioplasty.

Asprin antiplatelet dosage: 5-10 mg/kg orally at 24-48 hr intervals; Cat 75 mg orally once in 2-3 days.

The other antiplatelet drugs include abciximab, ticlopidine, clopidogrel and epoprostenol ($PGI_2$/prostacyclin analog). Ginger is also believed to prevent platelet aggregation (inihibition of $TXA_2$ synthesis) and prolong bleeding time.

**Fibrinolytic drugs** help in fibrinolysis and are used to open the occluded coronary artery (atherosclerotic plaque) in acute myocardial infarction. The drugs are Plasminogen Activators: Streptokinase and streptodonnase (Streptococcal proteins) and urokinase and Plasmin Activators: Recombinant anistreplase, alteplase, duteplase and reteplase. Alteplase is the enzyme of human melanoma. Alteplase helps in dissolution of existing clot (binds to fibrin of the clot and activates conversion of plasminogen to plasmin. Plasmin lyses fibrin and the clot without fibrin disintegrates). Reteplase and streptokinase break Arg-Val bond of plasminogen to form plasmin.

EXERCISE

1. What are cardiac glycosides? List them along with source. Describe how cardiac glycosides reverse the events of CHF.
2. Give the source of cardiac glycosides. Describe the mechanism of their cardiotonic and pharmacological effects.
3. What are dysrrhythmics (antiarrhythmics)? Give their classification and discuss the pharmacological basis of their cardiac actions.
4. Classify the anticoagulants of blood. Discuss in brief their mode of anticoagulant action.
5. **Write a short note on the following**:Digitalization
   a) Cardiac stimulants
   b) Antihypertensive drugs
   c) Hematinics
   d) Physiological hemostatics
   e) *In vivo* coagulants
   f) Systemic hemostatics
   g) *In vitro* coagulants
   h) *In vitro* hemostatics
   i) Vasodilators
   j) Antiplatelet drugs
   k) Fibrinolytics
   l) Signs of digitalization and digitalis toxicity

6. **Differentiate between the following:**
   a) Cardiotonics and cardiac stimulants
   b) *In vivo* and *in vitro* anticoagulants
   c) *In vitro* and systemic hemostatics
   d) Ionotropics and chronotropics
   e) Class I and Class III dysrrhythmics
   f) Class II and Class IV dysrrhythmics
   g) Sugar and genin or aglycone
   h) Rapid digitalization and intensive digitalization
   i) Slow digitalization and intensive digitalization
   j) Slow digitalization and rapid digitalization
   k) Digitalization and maintenance dose of cardiac glycosides
   l) Loading dose and maintenance dose of cardiac glycosides
   m) Positive ionotropic effect and positive chronotropic effect

7. **Write the mechanism of action of the following:**
   a) Digitoxin/Strophanthin/Ouabain
   b) Cardiac glycosides
   c) Quinidine/Disopyramide/Procainamide
   d) Lidocaine/Phenytoin/Mexiletine
   e) Flecainide/Encainide/Indicainide
   f) Amiodarone/Bretylium/Satolol
   g) Verapamil/Diltiazim/Nifedipine
   h) Methyldopa/Clonidine
   i) Cromokalim/Minoxidil/Nicorandil
   j) Nitroglycerin/Sildenafil
   k) Enalakiren
   l) Captorpril/Enalapril/Benezapril
   m) Saralasin/Losartan
   n) Hydralazine
   o) Nitrates (Vasodilatation)
   p) Alteplase/Reteplase/Streptokinase

8. **Give the line of treatment of the following; name the drug you recommend along with its dose and route of administration:**
   a) Cardiac fibrillation in a horse/cow
   b) CHF in a bullock/cat/dog
   c) Tachycardia in a dog/cat
   d) Anaemia in piglets/dog/cat/cattle
   e) Hemorrhagic syndrome in dog/cat/cattle
   f) To arrest post operative bleeding
   g) Myocarditis in a dog/cat
   h) Cardiac arrest in dog/cat
   i)

9. **Define the following (What do you mean the following?); give one example wherever necessary:**
   b) Cardiac stimulant
   c) Cardiotonic
   d) Ionotropic effect
   e) Chrontropic effect
   f) Hematinic
   g) Erythropoietin
   h) Hemostatic
   i) Fibrinolytic
   j) Antiplatelet drug

10. **ive the source of the following drugs:**
   a) Gitalin
   b) Strophanthidin
   c) Ouabain
   d) Heparin
   e) Hirudin
   f) Streptokinase
   g) Streptodonase
   h) Anistreplase
   j) Digitoxin/digoxin/ gitoxin

11. **Matching** (parallel pairs)/**Multiple choices** (right choices):
   a) Cardiotonic: Digitalis/Ouabain/Strophanthidin/Digitoxin/Gitoxin/Gitalin
   b) Aglycone: Pharmacological activity/Genin/Digoxigenin
   c) Sugar: Solubility of glycoside/Cell permeability of glycoside
   d) Digitalization effect: Positive ionotropism/Increase in force of contraction/Decrease in heart rate/Reduction in heart size/Diuresis/Relief of oedema/Reduction in sympathetic tone/Increase in cardiac out put/Reduced end diastolic pressure/Reduced venous pooling
   e) Loading dose: Digitalization dose
   f) Maintenance dose: Sustains effect
   g) Parenteral digitalization: Ouabain
   h) Oral digitalization: Digoxin/Digitoxin/Gitoxin/Gitalin
   i) Cardiotonics: Positive ionotropic effect/Negative chronotropic effect/Inhibition of $Na^+/K^+$ ATPase/No extra increase in oxygen demand/CHF
   j) Cardiac stimulants: Positive ionotropic effect/Positive chronotropic effect/No change in heart size/Increase in oxygen demand/Acute heart failure
   k) Cardiac stimulants: Adrenaline/Parasympatholytics/Xanthine derivatives/Calcium ions/Increased cAMP/Inhibiion of PDE/Adrenoceptor agonists
   l) Class I dysrrhythmics: Na channel blockers/Prevent cardiac depolarization/Quinidine/Procainamide/Dispyramide/Lidocaine/Phenytoin/Mexilitine/Flecamide/Encainide/Indecanide
   m) Class II dysrrhythmics: Negative ionotropic effect/Negative chronotropic effect/Beta-adrenoceptor blockers/Propranolol/Nadolol/Temolol
   n) Class III antidysrrhythmics: Prolong MAP/K channel block/Increase in refractory period/Amiodarone
   o) Class IV antidysrrhythmics: Ca channel block/No activation of actomyosin complex/Verapamil/Amlodipine/Diltiazim/Nifedipine

p) Signs of digitalization: Diuresis/Reduction in oedema/Relief of coughing/Increase in PR interval/ Decrease in QT interval/Change in direction of T wave
q) Signs of over digitalization: Anorexia/Palpitation/Tachycardia/Premature beats/Necrosis of myocardium
r) PDE inhibitors: Methylxanthines/Bipyridines/Benzimidazoles/Amrinone/Milrinone/Pimobendan/ Caffeine/Aminophylline/Increase cAMP
s) Antihypertensives: Alpha-adrenoceptor blockade/Adrenergic neuron blockers/Vasdilators/ Phentolamine/Nitroglycerin/Ca channel blockers/Antagonism of Renin-Angitensin
t) Ca Channel blockers: Nifedipine/Diltiazem/Verapamil/Nicardipine/Felodipine/Nimodipine/Amlodipine
u) K channel activation: Cromkalim/Minoxidil/Nicorandil/Hyperpolarization
v) NO donor: Nicorandil/Nitroprusside
w) Sildenafil: Inhibition of cGMP
x) Antiangina drug: Amyl nitrite/Nitro glycerin/Isosorbide/Dipyridamole
y) Renin Inhibitor: Enalakiren
z) ACE inhibitor: Captopril/Enalapril/Ramipril/Perindopril/Benazapril/Trandolapril
aa) Angiotensin antagonist: Saralasin/Lasratan
bb) Erythropoietin: Renal peritubular cells/Bone marrow stimulant/Proliferation of eryhthroids/formation of haemoglobin/Maturation of eryhthroblasts/Anaemia of chronic renal failure
cc) Local hemostatics: Adrenaline/Thromboplastin/Thrombin/Fibrin/Fibrinogen (all others of 'dd')
dd) Natural hemostatics: Thromboplastin/Thrombin/Fibrin/Fibrinogen/Gelatin sponge/Calcium alginate/ Oxidized cellulose/Silver nitrate/Tannic acid
ee) Systemic hemostatics: Vitamin K/Mixture of malonic and oxalic acids/Protamine sulfate
ff) *In vitro* anticoagulants: Sodium oxalate/Sodium Citrate/Sodium EDTA/Heparin
gg) *In vivo* anticoagulans: Heparin/Warfarin/Pindone/Anisodene/Acenocoumarol/Phencoumon/Dicoumarol
hh) Chelation of Ca ions: Sodium EDTA
ii) Insoluble Ca salts: Sidium citrate/Sodium oxalate
jj) Heparin: Activation of Plasma antithrombin III/Physiological anticoagulant
kk) Hirudin: Leech
ll) Hirugen: derivative of leech anticoagulant/Hirudin
mm) Argatroban: Competitive inhibitor of thrombin/Antithrombin
nn) Hydroquinone: Carboxylation of Factors II, VII. IX and X
oo) Oral anticoagulants: Functional deficiency of vitamin K
pp) Aspirin: Prevention of $TXA_2$ synthesis/Inhibition of COX I/Antiplatelet aggregation
qq) Plasminogen activator: Streptokinase/Streptodornase/Streptococcal proteins/Urokinase/Anisreplase/ Alteplase/Duteplase
rr) Antiplatelet drugs: Aspirin/Dipyridamole/Ticlopidone/Epoprostenol/$PGI_2$
ss) Inhibition of plasminogen to plasmin: Epsilon aminocaproic acid/Tranexamic acid
tt) Bepridil: Ca channel antagonis/Block both K and Na channels/Antiarrhythmic
uu) Monoxidil/Hydralazine: Arteriolar vasodilator
vv) Esmolol/Propranolol (Antiarrhythmic): Reduce Ca influc into AV node/Bl antagonist/Reduce cardiac excitability
ww) Bretylium/Dfetilide/Ibutilide (antiaarhythmic): Prolongs cardiac action potential/Increase intracardiac K/Increases K influx/Blocks K efflux
xx) Enoxoparin: Heparin of porcine origin
yy) Danaparin: Heparinoid anticoagulant
zz) Anisindione: Acts like warfarin
aaa) Ticlopidine/Asprin/Indomethacin/Clopidogrel/Abciximab/Ginger: Inhibits platelet aggregation
bbb) Alteplase: Enzyme of human melanoma/Plasmingen activator/Lysis of clot/Binds to fibrin
ccc) Alteplase/Reteplase/Streptokinase is used in treating thomboembolic disease.

12. **Substantiate each of the following by giving the most appropriate reason/explanation in one or two sentences:**
a) Ouabain is not used for oral digitalization.
b) Parenteral digitalization is followed in ruminants.
c) Heparin is called physiological anticoagulant.
d) In cardiac glycosides the positive ionotropic action resides in aglycone/genin/nonsugar part, but the sugar part also contributes to the outcome of effect.
e) Cardiotonics are used in treating a failing heart.
f) Cardiac glycosides reduce size of the enlarged heart and increase cardiac out put in CHF patients.
g) Strong positive ionotropic action is the saluatory effect of cardiac glycosides in CHF.
h) ACE inhibitors/Enalapril or benezapril can also be used along with cardiac glycosides in treating CHF.

i) Diuretics are used along with cardiac glycosides in treating CHF.
j) Qunidine enhances the effects of cardiac glycosides.
k) Diuretics/glucocorticoids promote digitalis-induced hypokalemia.
l) Ouabain is preferred for emergency digitalization
m) Dopamine can also be used to treat CHF.
n) Dobutamine is preferred to dopamine in treating CHF.
o) Methylxanthines/Theophylline/Amrinone/Milrinone/Pimobendan can also be used in dogs with CHF.
p) Cardiac stimulants are used in treating acute cardiac arrest.
q) Adrenaline/Isoprenaline is used in treating acute cardiac arrest.
r) Methylxanthines/Theophylline/Aminophylline is used in CHF and acute cardiac arrest.
s) Calcium borogluconate/Calcium chloride is used in preventing acute cardiac arrest.
t) Cardiotoncs, but not cardiac stimulants. are the preferred drugs in treating CHF.
u) Cardiac stimulants, but not cardiotonics are the preferred drugs in preventing acute heart failure.
v) Quinidine/procainamide/dyspyramide is effective in tachyarrhythmia.
w) Class I antidysrrhythmics act through preventing MAP.
x) Class II antidysrrhythmics cause negative ionotropic as well as effects.
y) Class III antidysrrhythmics prolong the depolarization phase of MAP.
z) Class IV antidysrrhythmics reduce myocardial contractility by interfering with activation of actomyosin complex in myocardial cells.
aa) Methyldopa/Clonidine cause hypotension.
bb) Phentolamine/Reserpine/Carbidopa/Methyldopa causes hypotension.
cc) Verapamil/Cromokalin/Nitroglycerine causes vasodilation.
dd) Enalapril/Captopril/Saralasin causes vasodilation
ee) Nitrates as antiangina drugs are better than dipyridamole
ff) Hydralazine is used as an antihypertensive drug.
gg) Ferrous sulfate/Copper sulfate/Cobalt chloride/$B_{12}$/Folic acid is used to treat anaemia/as hematinic.
hh) Erythropoietin is indicated in anaemia due to chronic renal failure.
ii) Chronic renal failure also leads to anaemia.
jj) Though thromboplastin/thrombin/fibrin/fibrinogen promotes blood coagulation, should not be administered systemically to treating haemorrhages.
kk) Ferric sulfate/silver nitrate/tannic acid arrest surface bleeding.
ll) Vitamin K is used prophylactically in bleeding disorders.
mm) Malonic and oxalic acids mixture/Protamine sulfate can be used to promote systemic blood coagulation.
nn) Sodium citrate/Sodium oxalate/Sodium EDTA cannot be used as a systemic blood anticoagulant.
pp) Heparin can be used as an *in vitro* or *in vivo* blood anticoagulant.
qq) Heparin in the body helps in preventing intravascular blood clotting.
rr) Coumarin/Indanedione derivatives act as systemic blood anticoagulants.
ss) Sweet clover poisoning is characterized by hemorrhagic syndrome.
tt) Hirudin/Hirugen/Argatroban exerts blood anticoagulant effect.
uu) Oral anticoagulants act in a manner similar to functional vitamin K deficiency.
vv) Prolonged use of aspirin promotes bleeding.
ww) Streptokinase/Streptodomase/Urokinase/Alteplase is used in angina.
xx) Leech causes bleeding.
yy) Nitroprusside toxicity resembles CN toxicity
zz) Nitrites exert antiplatelet/antithrombotic action.
a) Nitrates cause vasodilatation.
b) Epoprostenol (Prostacyclin analog) is used to treat pulmonary hypertension.
c) Anisindione causes haemorrhages.
d) Warfarin's/Anisindione's anticoagulant action is delayed.
e) Asprin/Indomethacin inhibits platelet aggregation and vasoconstriction.

# Chapter – 24: DRUGS ACTING ON RESPIRATORY SYSTEM

## 1. Antitussives

Are drugs which help in suppressing or relieving cough. Cough has a protective role mediated by medullary cough centre. It is of two types: Productive cough (secretion of sputum) and Non-productive cough or dry cough (not accompanied by secretions, mainly due to persistent/recurrent irritation in bronchi). Persistent coughing is highly distressing and exhaustive, especially the unproductive coughing which is also painful.

**Classification**: Based on site of action:

A. **Reflexly or Peripherally Acting:** Depress the tracheal and bronchial afferent sensory nerves and pulmonary stretch receptors and thus prevent their activation of medullary cough centre.
Benzonatate: Chemically related to tetracaine, exerts local anaesthetic effect on cough receptors in the respiratory tract.

B. **Centrally Acting:** Suppress cough through direct depression of medullary cough centre. Opioids are commonly used central antitussives:
   1) Codeine (methylmorphine): Horse and Cattle: 0.2-2 gm orally; Dog: 10-60 mg SC or 1-2 mg/kg orally 3 to 4 times in a day.
   2) Pholcodeine (a codeine derivative) has longer duration of action
   3) Dextromethorphan: Its actions are not through opioid receptors; may be directly depressing the cough centre. It is the dextroisomer of levorphanol, with no analgesic or addiction property. It can be used safely in cat. Dog and cat: 0.5-1 mg/kg orally 3-4 times a day.
   4) Butorphanol: An oipoid-agonist-antagonist with more potent analgesia than morphine and antitussive action than codeine (100 times): Dog: 0.05-0.1 mg/kg SC or 0.5-1 mg/kg orally 3-4 times a day.
   5) Hydrocodone: More potent than codeine: Dog: 0.25 mg/kg orally 3-4 times in a day.
   6) Noscapine: Benzylisoquinoline opium alkaloid having smooth muscle relaxant, with neither narcotic nor addiction properties, but has antitussive action like codeine. It causes histamine release in large doses.

## 2. Expectorants

Are drugs (Mucokinetics), which increase the fluidity (liquify) and volume of bronchial/pulmonary secretions (sputum) and help in their easy expulsion through coughing (productive). These drugs also help in promoting pulmonary drainage during inflammation of respiratory tract (pneumonia and bronchitis).

**Classification**: Basing on mode of action:

A. **Inhalation Expectorants:** Water steam, benzoin and volatile oils like eucalyptus oil and turpentine oil. Increase bronchial secretions by a direct local action. Give relief in chronic respiratory disease.

B. **Sedative Expectorants:** Act by stimulating mucus secretion in bronchi, which protects and reduces acute inflammation of respiratory passages. These have little antitussive activity:
   a) **Saline Expectorants:** Increase mucus secretion in respiratory passages reflexly from GIT: Ammonium carbonate, ammonium chloride and potassium iodide.
   b) **Demulcent Expectorants:** These have soothening action in upper respiratory passages (pharynx): Syrup, Balsam of Tolu, vasaka syrup.
   c) **Nauseant Expectorants:** Increase respiratory secretions by producing nausea: Ipecac orally @ 1 mg/kg.

C. **Stimulant Expectorants:** Stimulate and promote repair of chronic inflammatory process: Guaiacol and guaifensin (oral); Eucalyptus oil and terpentine oil (inhalation)

D. **Anodyne Expectorants:** Increase respiratory secretions by about 400%, reflexly through GIT. Also have antitussive action and pain relieving action: Camphorated tincture of opium (paregoric).

**Mucolytics:** These are drugs, which loosen or break viscous or inspissated pulmonary secretions to facilitate expectoration:

a) 10-20% solution of sodium acetyl cysteine as nasal spray or aerosol.
b) Bromhexine obtained from *Vasaka* plant (*Adhatoda vasica*) depolymerizes mucopolysaccharide: 1mg/kg twice a day orally or parentarally for 5-7 days in small animals; 0.1 – 0.25 mg/kg orally or paranterally for 7 days in horses.

### 3. Bronchodilators

Are drugs which relax the smooth muscles of bronchi, cause dilatation of respiratory passages and help in relieving bronchial asthma and acute respiratory distress. Acute asthma may be due to hyperparasympathomimetic activity or liberation of excess histamine. Autacoids like 5-HT, prostaglandins and leukorienes are also involved in the genesis of asthmatic attacks. In all the instances the basic cause intense constriction of bronchi.

**Classification**: Based on mode of action in relaxing the bronchi:

A. **Sympathomimetics:** $\beta_2$-adrenoceptor agonists (salbutamol, terbutaline, bambuterol, salmeterol, formoterol, fenoterol, pirbuterol etc), ephedrine and epinephrine (life saving in allergy/anaphylaxis). $\beta_2$ adrenoceptor activation is physiological antagnism of bronchospasm of any cause. These also inhibit release of bronchospasmogens histamine, cysteinyl-leukotrienes, $PGD_2$ and PAF from mast cells and TNFα, one of the main mediators of inflammation. In addition, these drugs may also increase ciliary action in clearing mucus.
B. **Xanthines/Methylxanthines:** Caffeine, theobromine, theophylline, aminophylline, etamiophylline etc. Direct relaxant action on bronchial smooth muscles, inhibition of phosphodiesterase with resultant increase in cAMP. Aminophylline in dogs @ 10 mg/kg every 6 hr or 6 mg/kg at 12 hr intervals orally.
C. **Parasympatholytics:** By blocking cholinergic muscarinic receptors: Ipratropium, atropine (30-100 microgram/kg SC).
D. **Antihistamines ($H_1$ antagonists):** Promethazine and diphenhydramine.
E. **Cromolyn:** Its bronchial relaxant action is believed to be multifacial: inhibition of histamine and leukoriene release, $\beta_2$-adrenoceptor activity, inhibition of action of PAF (antiinflammatory actions). Horse: 80 mg nebulization (inhalation with the help of a mask).
F. **Cysteinyl-Leukotriene Receptor Antagonists:** Zafirlukast and montelucast. Act by preventing leukotriene-induced bronchoconstriction.
G. **Antiinflammatory Agents:** Synthetic Analogues of Glucocorticoids: Beclomethasone dipropionate, budesonide and fluticasone propionate (used in man through inhalers): These act by reducing the formation of cytokines, inhibition of formation of $TXA_2$, $LTC_4$ and $LTD_4$ and leucocyte chemotaxins $LTB_4$ and PAF. In chronic asthma cases in man prednisole (oral) along with above inhalers or in status asthmaticus IV hydrocortisone is also recommended.
   **Prednisolone:** Horse: 0.5-1 mg/kg orally on alternate days; Cat: 1mg/kg/day
   For relief from chronic pulmonary obstructive disease in horse synthetic corticosteroid analogs like budenoside, beclomethasone dipropionate, flunisolide etc are also available in inhaler form.

Bronchodilaors are also used in chronic obstructive pulmonary disease in horses.

### 4. Analeptics

Are drugs which stimulate the depressed medullary respiratory centre (MRC) used for relieving respiratory insufficiency (Respiratory Stimulants), especially due to over dosage of anaesthetics or other CNS depressants.

A. **Doxapram**: Drug of choice in emergency cases. Acts by direct stimulation of MRC and Indirectly through excitation of carotid-aortic body chemorecptors: Horse: 0.5-1 mg/kg IV; Dog and Cat: 1-5 mg/kg IV; Foals 0.02-0.04 mg/kg IV.
B. **Nikethamide**: First respiratory stimulant. Stimulates directly the depressed MRC: Dogs: 2-4 mg/kg orally, IV or IM, repeat if required.

C. **Methyl Xanthines**: Caffeine, thephylline or aminophylline stimulate MRC: Theophylline: Dog: 11 mg/kg IM; aminophylline: Dog: 12 mg/kg as loading dose and 5 mg/kg as maintenance dose IM.

## EXERCISE

1. What are bronchodilators? What is their clinical application? Give their classification and write in brief the pharmacology of each group.
2. **Write a short note on the following**:
   a) Antitussives b) Expectorants c) Bronchodilators d) Analeptics
3. **Differentiate between the following**:
   a) Antitussive and expectorant
   b) Antitussive and antiasthmatic
   c) Central antitussive and reflex antitussive
   d) Sedative and stimulant expectorants
   e) Anodyne and stimulant expectorants
   f) Mucolytic and mucokinetic
   g) Productive cough and Nonproductive cough
4. **Define the following and give on example for each**:
   a) Antitussive b) Expectorant c) Antiasthmatic d) Analeptic e) Mucolytic f) Mucokinetic
5. **Matching** (Parallel pairs); **Multiple choices** (Right choices):
   a) Benzonatate: Reflex/Perpheral antitussive/Desensitizes cough receptors
   b) Opoid antitussive: Codeine/Phlocodeine/Dextromethorphan/Butorphanol/Hydrocodone/Noscapine
   c) Histamine liberator: Codeine/Noscapine/dTC/Amphotericin B/Allergic reaction/Anaphylactic reaction
   d) Noscapine: Smooth muscle relaxant/No addiction/Nonnarcotic/Antitussive/Histamine release
   e) Inhalation expectorant: Benzoin/Eucalyptus oil/Steam
   f) Saline expectorants: Ammonium carbonate/Ammonium chloride/Potassium iodide
   g) Demulcent expectorant: Vasaka
   h) Nauseant expectorant: Ipecac
   i) Stimulant expectorant: Guaiacol/Guaifenesin/Eucalyptus oil/Turpentine oil
   j) Paregoric: Camphorated tincture of opium
   k) Mucolytic: Sodium acetyl cysteine/Bromohexine/Vasaka
   l) Bronchodilator: Salbutamol/Ephedrine/Aminophylline/Ipratropium/Cromolyn/Zafirlukast/Beclomethasone
   m) Bronchospasmogen: Histamine/Cysteinyl leukotrienes/PGD2/PAF
   n) Bronchial asthma: Beta2-adrenoceptor agonists/Ephedrine/Parasympatholytics/Antihistamines/Leukotriene antagonists
   o) Leuokotriene antagonist: Zafirlukast/Montelucast
   p) Cromolyn: Bronchial relaxation/Inhibition of histamine release/Inhibition of leukotriene release/ Inhibition of action of PAF/Beta2-adrenoceptor activity
6. **Give the source of the following**: a) Vasaka b) Ipecac
7. **Write the mechanism of action of the following drugs**:
   a) Doxapram b) Nikethamide c) Cromolyn d) Salbutamol
   e) Ephedrine f) Theobromine g) Zafirlukast h) Prednisolone
   i) Vasaka
8. **Suggest the line of treatment of the following; mention the drug, it dose and route of administration**:
   a) Barbiturate over dosage in a dog/cat c) Asthma in a horse/dog/cat
   b) Cough in a dog
9. **Give the most appropriate reason in one or two sentences for each of the following statements**:
   a) Benzonatate desensitizes cough receptors in the respiratory tract.
   b) Opioids have strong antitussive action.
   c) Noscapine though an antitussive causes respiratory distress in large doses.
   d) Expectorants give relief in productive cough
   e) Inhalation expectorants give relief in chronic respiratory disease.
   f) Glucocorticoids or their analogs are used in asthma.
   g) Cromolyn inhalers are used in asthma.
   h) Methxanthines/Theobromine are used in bronchial asthma.
   i) Zafirlukast/Motelucast is used in bronchial asthma.
   j) Analeptics: Doxapram/Nikethamide/Theophylline/Aminophylline
   k) Analeptics are used in overdosage of anaesthetics.
   l) Promethazine/Diphenhydramine/Ephedrine/Salbutamol gives relief in bronchial asthma.

# Chapter – 25: DRUGS ACTING ON URINARY SYSTEM AND FLUID THERAPY

## 1. Diuretics

Are drugs which promote urine formation and its excretion, augmenting $Na^+$ and water loss from the body. The main effect of diuretics is to reduce renal tubular reabsorption of $Na^+$ and $Cl^-$ leading to secondary water loss.

**Classification:** Based on mode of action

A. Osmotic diuretics
B. Carbonic anhydrase inhibitors
C. Natriuretic diuretics
D. Acidifying salts
E. Aldosterone antagonists
F. Mercurial diuretics
G. Potassium sparing diuretics
H. Loop diuretics
I. Xanthine diuretics

**Osmotic Diuretics:** These are pharmacologically inert substances like mannitol which are filtered through the glomerulus, but not absorbed in the tubules. The unabsorbable solute in the tubular fluid exerts osmotic action, passive reabsoroption of water in the proximal tubule is prevented (one molecule of mannitol withholds six molecules of water). This has secondary effect on $Na^+$ reabsorption. Since more water is withheld, the $Na^+$ concentration becomes lesser, than what it would have been normally (without mannitol), reducing $Na^+$ reabsorption, causing some $Na^+$ loss through urine. Therefore mannitol causes primarily a water diuresis, with relatively smaller natriuresis. Mannitol is not absorbed orally; given IV as 5-10% solution @ 1-2 mg/kg. Mainly used in acute renal failure to maintain GFR and urine flow for forced diuresis (in cases of poisonings: to promote enal excretion of metabolites of toxicants), glaucoma and cerebral oedema.

**Carbonic Anhydrase Inhibitiors:** Acetazolamide, methazolamide and dichlorphenamide. These reversibly inhibit the enzyme carbonic anhydrase, which normally catalyzes formation of carbonic acid which splits to form $HCO3^-$ and $H^+$ in proximal tubular epithelial cells. The $H^+$ are secreted into tubular lumen in exchange of $Na^+$, causing $Na^+$ reabsorption. When the enzyme is inhibited, $H^+$ are not available for reabsorption of $Na^+$, which are excreted along with water causing diuresis accompanied by natriuresis.

**Natriuretic Diuretics:** Thiazide diuretics (Hydrochlorthiazide, bendroflumethiazide, cyclopenthiazide and newer compounds like chlortalidone, indapamide, xipamide and metolazone). These drugs act on the distal tubule inhibit $Na^+/Cl^-$ cotransport from the tubular lumen (active reabsorption), by binding to the cotransport system, causing diuresis accompanied by excretion of NaCl. The thiazide diuretics also cause vasodilatation ($Na^+$ loss and direct relaxant efect) and hyperglycaemia (inhibition of insulin secretion). $Na^+$ is also accompanied by loss of $K^+$.

**Acidifying Salts:** Ammonium chloride after absorption is metabolized to form $H^+$, $Cl^-$ and urea. The accumulated $Cl^-$ displaces $HCO_3^-$ from $NaHCO_3$ and $KHCO_3$ forming NaCl, KCl and $HCO_3^-$. The $H^+$ combine with $HCO_3^-$ yielding $H_2CO_3$, which splits to $CO_2$ and $H_2O$ under the influence of carbonic anhydrase. Neutralization of bicarbonate and formation of carbonic acid/$CO_2$ result in metabolic acidosis. Thus higher concentration of NaCl, Kcl and urea exert increased osmotic tension in renal tubular fluid causing osmotic diuresis.

$$2NH_4Cl \rightarrow 2H^+ + 2Cl^- + \text{Urea}$$

$$KHCO_3 \text{ and } NaHCO_3 + 2H^+ \rightarrow 2HCO_3^- + Na^+ \text{ and } K^+;$$

$$2HCO_3^- + H^+ \rightarrow H_2CO_3 \rightarrow H_2O \text{ and } CO_2$$

$$Na^+ \text{ and } K^+ + 2Cl^- \rightarrow NaCl \text{ and } KCl$$

Urea, NaCl and KCl, exert osmotic action in tubules and are excreted through urine along with water.

**Aldosterone Antagonists:** Spironolactone, eplerenone and canrenone. Aldosterone in collecting tubules promotes $Na^+$ reabsorption and $K^+$ excretion. It activates the $Na^+$ channels to open, causing rapid reabsorption of water into the tubular cells, from where $Na^+$ enter into blood in exchange of $K^+$ ($Na^+/K^+$ ATPase system). Aldosterone also stimulates synthesis of a specific protein which activates $Na^+$ ion channels through which $Na^+$ enter blood. The antagonists competitively prevent the action of aldosterone combining with the $Na^+$ channel receptor resulting non-opening of the channel leading to failure of reabsorption of $Na^+$ from the lumen of collecting ducts, causing diuresis accompanied by significant natruresis.

**Mercurial Diuretics:** Mercurous chloride (calomel), meralluride, mersalyl, merbaphen, mercurophylline, mercumatilin, chlomerodrin etc. Act through formation of mercuric ions in the tubular epithelial cells. These ions combine with cysteine present in –SH containing enzymes associated with ion transport system mechanisms operating in proximal portion of distal tubules preventing $Na^+$, $K^+$ and $Cl^+$ reabsorption from the tubule lumen causing diuresis. These are no longer recommended due to chances of renal damage.

**Potassium Sparing Diuretics**: Amiloride and triamterene. These act by blocking luminal of Na+ channels (through which aldosterone increases Na+ reabsorption), prevent Na+ reabsorption in the collecting tubules and decreasing K+ excretion. Amiloride inhibits Na+/K+ ATPase in distal convoluted tubules (DCT) and prevents reabsorption of Na+ in exchange of K+. Na+ is eliminated accompanied with water diuresis. Triamterene stabilizes membrane potentials on luminal phase in DCT (but not Na+/K+ ATPase) and prevents exchange of Na+ and K+ causing Na+ elimination and water diuresis.

**Loop Diuretics:** Furosemide, bumetanide, piretanide, torasemide, ethacrynic acid etc. The site of action of these diuretics is ascending loop of Henle, considered as the most powerful diuretics. These drugs prevent the cotransport of Na+ and Cl- from the tubular lumen into the tubular cells (from there into interstitial space) by inhibiting the Na+/K+/2Cl- carrier located in the luminal membrane. Increased Na+ loss is also accompanied by increased loss of both H+ and K+, resulting in diuresis, metabolic alkalosis and hypokalemia (hypokalemia and hypocalcaemia). These diuretics reduce aldosterone secretion (increase in K loss) and plasma volume. Potassium salts are to be supplemented along with loop diuretics to compensate hypokalemia. It is also advisable to give potassium sparing diuretics along with loop diuretics. Furosemide also causes hyperuremia and gout by decreasing renal excretion of uric acid.

**Xanthine Diuretics:** Theophylline, aminophylline and caffeine. These cause diuresis indirectly, improving the cardiovascular haemodynamics: Cardiac stimulation, increased cardiac out put, increased renal blood flow and increased GFR. In addition these also inhibit the action of ADH in the collecting tubules. Theophylline is the most potent.

**Clinical Uses of Diuretics:**

1. To relieve oedema of nephritic, hepatic or cardiac origin (CHF, in conjunction with cardiac glycosides and/or ACE inhibitors).
2. In ascites of nephritic or hepatic origin.
3. Oliguria due to renal disease.
4. To promote renal excretion of systemic toxicants.
5. Post-operative flush of urethra after removal of renal/urethral caliculi.

Doses and Administration of Diuretics in Animals

| Diuretic | Dose | Administration |
|---|---|---|
| Acetazolamide | 2 mg/kg<br>0.5 – 1 mg/kg | Orally once in a day<br>IM once in a day |
| Chlorthiazide | 10 – 15 mg/kg<br>1 mg/kg | Orally twice a day<br>IM or IV once in a day |
| Furosemide | 5 – 10 mg/kg<br>2 – 6 mg/kg | IM once or twice a day<br>IV once a day |
| Hydrochlothiazide | 0.5 – 1 mg/kg | Orally twice a day |
| Mannitol | Dog: 250 – 500 mg | 5-10% solution by slow IV, 2-5 ml/min |
| Spironolactone | Dog: 2.5-5 mg/kg | Orally twice a day |

## 2. Urinary Alkalizers

Are basic agents for alkalinization of urine. Alkalinization of urine promotes antibacterial action of certain antibiotics (aminoglycosides), excretion of acidic drugs and increasing the solubility and reducing the risk of sulfonamide renal toxicity (crystalluria) especially in carnivores. Urinary alkalizers also increase urinary excretion of salicylates. Basic salts such as sodium bicarbonate and those get converted to bicarbonate (sodium acetate or sodium citrate) are commonly used as urinary alkalizers. Dog: Sodium bicarbonate @ 0.5-1 gm thrice daily with large intake of water.

## 3. Urinary Acidifiers

Are drugs which cause acidification of urine. They help in increased excretion of basic drugs and enhance the antibacterial action of urinary antiseptics like hexamine and certain antibiotics (penicillins and tetracyclines).

Sodium acid phosphate: 0.2-0.3 gm or Ascorbic acid 250-500 mg or methionine 30 mg or chlorethamine 60-90 mg thrice daily orally.

Ammonium chloride may also be used as an urinary acidifier as it causes acid diuresis.

## 4. Urinary Antiseptics

Are drugs which exert antiseptic/antibacterial action in urinary tract. Sulfonamides, cotrimoxazole, nitrofurantoin and antibiotics like streptomycin, gentamicin, oxytetracycline and carbenecillin are commonly used in acute urinary tract infections. In chronic urinary tract infections hexamine (methenamine), mandelic acid (or its salts: ammonium mandelate or calcium mandelate), nitrofurantoin and nalidixic acid are used. Hexamine in acidic medium is broken into ammonia and formaldehyde (exerts antiseptic action). Urinary acidifiers (urine pH 5.5 or less) enhance the antibacterial activity of hexamine and hence are used prior to hexamine.

a) Hexamine (Methenamine): All species: 50 mg/kg orally. Administration of sodium acid phosphate 15-20 minutes prior to hexamine ensures acidificaion of urine.
b) Calcium mandelate: The mandelic acid salts are self-acidifying. Dog: 250 mg//kg orally.
c) Nitrofurantoin: Exerts broad spectrum activity in urinary tract, except against *Pseudomonas* and *Proteus*. Dog: 4 mg/kg orally thrice a day
d) Nitroxoline and Nalidixic acid: Have broad spectrum antibacterial activity including *Pseudomonas* and *Proteus*. Dog: Nitroxoline: 10 mg/kg orally; Nalidixic acid: 15-45 mg/kg orally in three divided doses in a day.
e) Antibiotics: Amoxicillin-clavulanic acid @ 12 to 25 mg/kg orally twice a day; cephalexin @ 22 mg/kg orally thrice a day; and trimethoprim-sulfadiazine @ 30 mg/kg.
f) Antifungal drugs: In treatment of candidal cystitis: Fluconazole in dog @ 2.5-5 mg/kg/day in two divided doses and in cat @ 50 mg/cat/day orally

## 5. Fluid and Electrolyte Therapy

Fluid therapy consists of administration of isotonic fluids to correct body's fluid imbalance. It is advocated in haemorrhages, vascular shock, anaemia, haemolysis, failure of blood clotting mechanisms and to provide specific antibodies against infections. The different fluids used are:

A. **Whole blood:** IV transfusion is done @ 20 – 35 ml/kg body weight. Cross matching is not necessary, except in horse, where there is no need of cross matching in the first instance, but subsequent transfusions need cross matching to prevent anaphylaxis. In anaemia, blood transfusion is done to raise the haemoglobin level to 10-12%.
B. **Blood Plasma:** IV transfusion is done @ 15 – 20 ml/kg body weight. It is indicated, when the body fluid component is lowered (normal cellular component) in conditions such as burns or dehydration.
C. **Blood Serum:** It is usually indicated for immunological purposes (IV administration of immune serum).

D. **Plasma Volume Expanders/Extenders:** These constitute artificial fluids isotonic to the plasma. Dextran-40 (administered IV as 6% solution in normal saline @ 10 ml/min; 20 ml/kg/day); gum acacia or gelatin (administered IV as 6% solution in normal saline).

Electrolyte Therapy is administration of special electrolyte solutions to correct hypovolaemia (dehydration/haemorrhage), over hydration (renal, hepatic or cardiac diseases), electrolyte imbalance (hypocalcaemia) and metabolic acidosis or alkalosis. Specific electrolyte therapy is recommended as per the clinical condition. The different electrolyte solutions are:

| Condition | Electrolyte Solution |
|---|---|
| Mild acidosis | 1.3% sodium bicarbonate in saline or 5% dextrose |
| Severe acidosis | 5% Sodium bicarbonate or Ringer's lactate |
| Acidosis and hyponatremia | Ringer's lactate + sodium bicarbonate @ 5 gm/liter |
| Alkalosis and hypokalemia | Potassium acidifying solution |
| Acidosis, alkalosis, loss of electrolytes and dehydration | Balanced electrolyte solution |

The volume of electrolyte solution to be administered (IV) is based on severity of the condition. In severe dehydration/hypovolaemia the replacement is to be done up to 15% body weight (50 ml/kg/hr in severe cases or 15-30 ml/kg/hr in less severe cases). Calcium solutions need to be administered slowly with caution, monitoring cardiac condition.

## EXERCISE

1. Classify the diuretics and indicate their site of action in the nephron. Write the clinical application of diuretics.
2. **Write a short note on the following:**
   a) Osmotic diuretics
   b) Carbonic anhydrase inhibitors
   c) Natriuretic diuretics
   d) Acidifying diuretics
   e) Aldosterone antagonists
   f) Mercurial diuretics
   g) Loop diuretics
   h) Urinary alkalizers
   i) Urinary acidifiers
   j) Urinary antiseptics
   k) Fluid therapy
   l) Electrolyte therapy

   **Describe the mechanism of action of the following drugs:**
   a) Mannitol (diuretic)
   b) Acetazolamide
   c) Hydrochlorthiazide
   d) $NH_4Cl$ (diuretic)
   e) Spironolactone
   f) Mersalyl
   g) Amiloride
   h) Loop diuretics
   i) Xanthine diuretics
   j) Methenamine/Hexamine

4. **Matching** (parallel pairs) or **Multiple choices** (Right choices):

a) Osmotic diuretic: Mannitol
b) Urinary acidifier: Sodium acid phosphate
c) Severe acidosis: Ringer's lactate
d) Plasma volume expander: Dextran-40
e) Acidifying diuretic: Ammonium chloride
f) Mild acidosis: 1.3% sodium bicarbonate
g) Urinary antiseptic: Hexamine/Ca mandelate/Nalidixic acid/Nitrofurantoin
h) Urinary alkalizer: Sodium bicarbonate/Sodium acetate/Sodium citrate
i) Carbonic anhydrase inhibitor: Actazolamide/Methazolamide/Dichlophenamide
j) Natriuretic diuretic: Hydrochlothiazide/Cyclopenthiazide/Bendroflumethiazide
k) Aldosterone antagonist: Spironolactone/Eplerenone/Canrenone
l) Mercurial diuretic: Calomel/Meralluride/Mersalyl/Merbaphen
m) Potassium sparing diuretic: Amiloride/Triamterene
n) Loop diuretic: Furosemide/Bumetanide/Piretanide/Ethacrynic acid/Torsemide
o) Xanthine diuretic: Theophylline/Amionophylline/Caffeine

5. **Give the clinical application of the following:**
   a) Diuretics
   b) Urinary alkalizers
   c) Urinary acidifiers
   d) Urinary antiseptics
   e) Fluid therapy
   f) Electrolyte therapy
   g) Methenamine
   h) Actazolamide
   i) Furosemide

6. **Give the line of treatment of the following; name the drug, its dose and route of administration:**
   a) Oedema of cardiac/renal/hepatic origin n a dog/horse
   b) Ascites of renal or hepatic origin in a dog/cow
   c) To promote renal excretion of toxicants in a horse/cat
   d) Urinary tract infection in a dog
   e) Severe acidosis in a cow
   f) Mild acidosis in a buffalo
   g) Oliguria in a dog
   h) Acidosis and hyponatremia in a cow
   i) Alkalosis and hypokalemmia in a buffalo
   j) Vascular shock/Hemorrhagic shock/Fluid loss/dehydration in a horse/dog

7. **Give the most appropriate explanation in one or two sentences for each of the following statements:**
   a) Mannital causes primarily a wate diuresis.
   b) Carbonic anhydrase inhibition results in diuresis.
   c) Natriuretic diuretics cause hyperglycemia/hypokalemia/fall in BP.
   d) Aldosterone antagonism leads to diuresis.
   e) Coffee or tea causes diuresis.
   f) Amiloride/Triamterene is called a potassium sparing diuretic.
   g) Prior administration of sodium bicarbonate/sodium citrate/sodium acetate enhances efficacy of aminoglycoside antibiotics while treating urinary tract infections.
   h) Prior administration of sodium bicarbonate/sodium citrate/sodium acetate reduces the risk of sulfonamide-induced renal toxicity.
   i) Prior administration of sodium acid phosphate/methionine/chlorethamine enhances efficacy of penicillins/tetracyclines while treating urinary tract infections.
   j) Urinary acidifers are administered prior to use of hexamine in treatment of urinary tract infections.
   k) Prior urinary acidification is not required in use of ammonium mandelate/calcium mandelate in treating urinary tract infections.
   l) IV blood transfusion/Fluid or electrolyte therapy should be done slowly.
   m) Urinary antiseptics like hexamine. penicillins. tetracyclines etc in general are more effective in carnivores.
   n) Mannitol causes mainly water diuresis accompanied by small natriuresis.
   o) Acetazolamide causes diuresis accompanied by natriuresis.
   p) Thiazide diuretics are not to be used in diabetes mellitus.
   q) Diuresis by loop diyretics (Furosemide) results in metabolic acidosis.
   r) Ammonium chloride can be used as urinary acidifier.
   s) Use of loop diuretics precipitates gout.
   t) Loop diuretics cause hypokalemia.
   u) Loop/Thiazide diuretics are combined with potassium sparing diuretics.
   v) Though diuretic effect of amiloride and triamterene is similar. their mechanism of diuretic action is not similar.

## Chapter – 26: DRUGS ACTING ON UTERUS

### 1. Oxytocics

Are drugs which exert stimulant action on uterine contractions, especially that of atonic or hypotonic parturient uterus; also called as ecbolics.

**Oxytocin**: An octapeptide hormone synthesized in supraoptic nucleus of hypothalamus and stored in posterior pituitary, from where it is released as per the physiologic needs. It has physiological role in initiating labour and ejection of milk.

**Release of oxytocin:**

1. Fetal and uterine stimuli at the time of parturition.
2. Vaginal stimulus during coitus.
3. Teat stimulus following suckling by the young one.

**Physiological Role:**

1. During coitus increases contraction of the female genital tract facilitating upward transport of semen.
2. Coverts weak, spontaneous and irregular contractions into forceful, regular and purposeful contractions at the time of parturition.
3. Causes milk let down, following teat stimuli contracting the mammary myoepithelial cells, but does not increase milk formation.

**Action on Uterus:** Oestrogen sensitized uterus (terminal pregnancy) is highly sensitive to oxytocin. It increases the force and frequency of uterine contraction (increased depolarization and $Ca^{++}$ influx in myometrial cells), independent of innervation.

**Action on Mammary Gland:** Milk let down in lactating animals by causing contraction of myoepithelial tissue.

**Action on Kidney:** In high doses increases water reabsorption in tubules and decrease urine out put (like ADH).

Oxytocin is inactive orally (being a protein) administered IV or I.M. One unit of oxytocin = 2 micrograms of pure oxytocin.

**Synthetic oxytocin Analogues:**

1. 1-Deamino-oxytocin: More potent than oxytocin
2. Arginine vasotocin: A peptide found in pituitary gland of many non-mammalian vertebrates. It has oxytocic and ADH actions.

**Clinical Uses of Oxytocin:**

1. For induction of labour: In small animals by slow IV infusion in dextrose solution @ 2 ml/minute till the onset of labour (Adequate cervical dilatation must be confirmed prior to use of oxytocics, if not rupture of uterus may occur).
2. In agalactic animals: For milk let down only, but does not increase formation of milk (not a galactagogue). Adrenaline neutralizes this action of oxytocin.
3. In cases of uterine inertia and for rapid involution of uterus.
4. To arrest post-parturient haemorrhage.
5. For expulsion of retained placenta.
6. Termination of unwanted pregnancy (in early stages).

**Doses of Oxytocin (Units)**

| Animal | Obstetric Use | Milk Let Down |
|---|---|---|
| Bitch | 5 – 25 | 2 – 10 |
| Cow or Mare | 75 – 100 | 10 – 20 |
| Sow or Ewe | 30 – 50 | 5 – 20 |

**Ergot Alkaloids**: Alkaloids from *Claviceps purpurea*. Ergometrine (or ergonovine) has prominent effect on uterus. It exerts direct powerful, long-lasting and spasmodic contractions on myometrium; also has vasoconstrictor effect. Not usually preferred for induction of labour (strong action on uterus and may cause foetal asphyxia due to vasoconstriction - reduced blood supply from placenta). Another alkaloid ergonovine also has oxytocic action. Its synthetic derivative methylergometrine has powerful ecbolic action, but lacks vasoconstrictor action.

Ergometrine is generally **indicated** for:

1. Control of post-parturient haemorrhage.
2. For rapid involution of uterus.
3. For expulsion of retained placenta.
4. Termination of pregnancy (very early stages).

**Doses of Ergometrine**: Mare or Cow: 1-3 mg; Ewe, Goat or Sow: 0.14-1 mg; Bitch: 0.2-0.5 mg; Cat: 0.07-0.2 mg IM.

**Prostagaldins ($PGE_1$, $PGE_2$ and $PGF_{2\alpha}$)**: Exert potent stimulant action on myometrium ($PGF_{2\alpha}$ also has luteolytic effect). Oxytocin is preferred over these, because of high cost and unreliability of effect due marked individual variation). $PGF_{2\alpha}$ @ 30-40 mg IM in large animals and @ 5-15 mg IM in small animals. $PGE_2$ analog: Dinoprostone; $PGE_2$ analogs: Gemeprost and Misoprostol and $PGF_{2\alpha}$ analogs: Dinoprost and carboprost are used in human medicine. Cyclooxigenase inhibitors (NSAIDs) delay parturition: due to inhibition of prostaglandin synthesis.

**Carbachol**: Potent cholinergic drug. Not a drug of choice for oxytocic use (due to other effects). May be used in Sow during mid farrowing @ 2 mg SC.

## 2. Tocolytics

Are uterine relaxants; inhibit uterine contractions by relaxing uterine smooth muscles. These drugs are used to delay the labour and stop threatened abortion. Basing on mechanism of action tocolytics are classified as:

1. **Selective $\beta_2$ adrenoceptor Agonists**: Relax uterine smooth muscles: Salbutamol, terbutailine, ritodrine and isoxsuprine. These drugs inhibit spontaneous as well as oxytocin induced uterine contractions.
2. **Calcium Channel Blockers**: Block $Ca^{++}$ influx in uterine smooth muscles, interfere with the action of contractile proteins (actomyosin) and prevent contraction of uterine smooth muscles: Nifedipine.
3. **Oxytocin Anatgonist**: Atosibin; a synthetic receptor antagonist. It is recently introduced to check uncomplicated premature delivery in women.

**Relaxin** is a decapeptide secreted by corpus luteum, placenta and uterus when the animal approaches parturition. Its physiological role in parturition includes softening/relaxation of cervix and pelvic ligaments and expansion of reproductive tract to ensure easy and safe parturition.

### EXERCISE

1. What are oxytocics? Classify the oxytocics and discuss their pharmacology.
2. What is oxytocin? Discuss its physiological role, pharmacology and clinical application.
3. **Write a sort note on the following**:
   a) Oxytocin b) Prostaglandins on uterus b) Tocolytics
4. Write the obstetrical **uses** of oxytocin/prostaglandins/tocolytics/ergometrine.
5. **Differentiate between** a) Oxytocic and tocolytic b) Oxytocin and relaxin.
6. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
   a) Oxytocin analogs: 1-Deamino-oxytocin/Arginine vasotocin
   b) Oxytocin antagonist: Atosibin
   c) $PGE_2$ analog: Dinoprostone
   d) $PGE_1$ analog: Gemeprost/Misiprostol

e) $PGF_2$alpha analog: Dinoprost/Carboprost
f) Tocolytics:Salbutamol/Terbutaline/Ritodrine/Isoxsuprine/Beta$_2$-adrenoceptor agonists/Ca channel blockers/ Nifedipine
g) $PGF_{2alpha}$: Oxytocic/Luteolytic
h) Oxytocic: Carbachol/Dinoprostone/Gemeprost/Misoprostol/Dinoprost/Carboprost/$PGE_1$/$PGE_2$/$PGF_{2alpha}$
i) Oxytocin: Formed in hypothalamus/Stored in posterior pituitary
j) Relaxin: Secreted from CL. placenta or uterus/Softens cervix/Softens pelvic ligaments/Expansion of reproductive tract
k) One unit of oxytocin: 2 microgram of pure oxytocin

7. **What is the source of** a) Oxytocin b) Arginine vasotocin c) Relaxin

8. **What treatment you suggest for the following conditions? Mention the drug, its dose and route of administration**:
a) Agalactia in a cow/bitch/ewe
b) Parturient uterine inertia in a bitch
c) Aid for rapid uterine involution in a cow
d) Uterine prolapse in a mare/bitch
e) To terminate prolonged gestation in a sow
f) To expel uterine debris in a goat
g) To expel retained placenta in a buffalo
h) To prevent premature labour in a bitch/goat

9. **Give the most appropriate reason for each of the following statements in one or two sentences**:
a) Oxytocin is a physiological ecbolic.
b) Oxytocin is used in agalactic animals.
c) Terminal pregnant uterus is highly sensitive to oxytocin.
d) Oxytocin at high dosage causes oliguria.
e) Oxytocin is administered by IV or IM injection.
f) Methylergometrine is superior to ergometrine for hastening parturition.
g) Ergometrine is not preferred for induction of labour. but used for other obstetrical purposes.
h) Tocolytics are used to prevent threatened abortion.
i) Beta$_2$ adrenoceptor agonists/Ca channel blockers are used as tocolytics.
j) Atosibin prevents premature labour.
k) NSAIDs delay parturition.
l) Administration of cortocosteroids in pregnant animals may cause abortion.
m) Carbachol is not a preferred oxytocic.
n) Cervical dilatation must be confirmed prior to obstetrical use of ecbolics/oxytocics.
o) Milk let down effect of oxytocin is neutralized in unduly excited cows.
p) Oxytocin is not a galactagogue.
q) Relaxin ensures easy or safe parturition.

## Chapter – 27: DURGS ACTING ON MUCOUS MEMBRANES AND SKIN

1. **Emollients:** These are inert oily agents which soften, soothen, lubricate and protect the skin or mucous membranes against irritation. They treat dryness of the surfaces by preventing evaporation of moisture. Often antimicrobial agents are added to the emollients.

A. Vegetable (fixed) oils: Olive oil, linseed oil, coconut oil etc.
B. Animal fats: Wool fat, lanoline or bees wax.
C. Hydrocarbons: Soft or hard paraffin, liquid paraffin, vaseline and white petroleum jelly.
D. Polyhydric alcohols: Glycerol, glycerin and propylene glycol.

2. **Demulcents:** These are inert substances which sooth and relieve irritation, primarily involving the inflammed/ injured mucous membranes. They form a protective layer over the irritated surfaces: Solutions of gum acacia, gum tragacanth, *Glycyrrhiza* root extract, methyl cellulose, propylene glycol and glycerine.

3. **Astringents:** These are the agents which precipitate the surface proteins, form a protective coating over the inflammed surfaces, skin or gastric mucosa. Astringents help in forming a protective layer or scab for proper healing of underlying wounds. These agents also help in stopping bleeding by hastening blood clot formation.

**A. On skin:**
a) White lotion (lead acetate 1 gm, zinc sulfate 750 mg and distilled water 20 ml). It also acts as a sedative lotion.
b) Aqueous solution of zinc sulfate (10%).
c) Zinc oxide ointment (20%)
d) Calamine lotion (Calamine 150 gm,zinc oxide 150 gm,glycerin 50 ml and distilled water to 1000 ml)
e) Paste containing copper sulfate 4 gm, zinc sulfate 4 gm and lead acetate 4 gm in enough water.
f) Dusting powder containing acacia bark 4 gm, neem bark 4 gm and camphor 2 gm.

**B. On Mucous Membranes:** Tannins (Tannic acid).

4. **Adsorbants and Protectives:** These are finely powdered inert, insoluble solids capable of inactivating the irritants by binding to them. They exert physical protection to skin or mucous membranes: Magnesium or zinc stearate, calamine, bentonite, starch, boric acid, zinc oxide etc.

5. **Antipruritics:** These are agents, which prevent irritation or itching, a common sign of many skin diseases. These are also called as skin/dermal sedatives.
Powders: Boric acid, calamine, starch, talc, zinc carbonate and zinc sulfate.
Lotions: Refrigerant lotions: White lotion, calamine lotion and ammonia lotion.
Antibacterial and antifungal antibiotics are also used in the form of solutions or ointments in treatment of skin diseases. Corticosteroid ointments are also used in skin affections due to their antiinflammatory action. Sometimes a local anaesthetic is also added to topical preparations to reduce pain sensation. Antihistamines (antagonize effects of histamine release in skin) are also added to antipruritic formulation.

6. **GI Mucosal Protectants:** These are agents which protect the intestinal mucosa against irritation by forming a protective layer, neutralizing the irritants or adsorbing the irritants: Kaolin, activated charcoal, bismuth carbonate etc.

7. **Keratolytics:** Are agents which dissolve the intercellular substance in the horny layer of the skin (keratinized) used in the treatment of hyperkeratosis (corns, warts, chronic dermatitis, ringworm etc):

a) Salicylic acid ointment in hyperkeratosis.
b) A solution containing 40% antimony trichloride 5% salicylic acid solution in distilled water or 3-5% salicylic acid in alcohol in treatment of hyperkeratosis.

c) A solution of salicylic acid 10-20% in alcohol for dissolving corns.
After keratolysis an astringent ointment or white lotion should be applied over the area.

**8. Caustics:** Are corrosives cause local tissue destruction sloughing and are used for destroying excessive granulation growth on skin or horn buds:

a) Phenol (80% water solution)
b) TCA (1-20% water solution)
c) Glacial acetic acid (pure)
d) Caustic pencil (toughened silver nitrate)
e) Copper sulfate (20% water solution)
f) Solution consisting of 10 gm arsenic trioxide, 100 ml of 5% potassium hydroxide and 28 ml dilute HCl in distilled water to 1000 ml

**Escharotics (cauterizers)**: These are like caustics cause local destruction of the tissue (moles/warts/papillomas or keratotic lesions), but in addition also help in formation of scab by precipitating exudates protein from wounds, preventing their infection and prmoting wound healing.

**9. Counter Irritants:** These are agents used to produce hyperaemia in an attempt to relieve pain and promote healing of tissues beneath the skin, after application over the surface (skin). When counter irritants are applied by massage or rubbing over the body, the sensory nerve endings in the area are stimulated causing reflex vasodilatation causing enhanced blood flow and augmenting healing processes. Application of counter irritants serves the purpose of sub-siding the existing pain as seen in arthritis, sprains, muscle soreness, stiffness of joints, headache etc. The pain sensation originating from the underlying deep tissues is masked by the sensory impulses originating from the cutaneous irritation produced by the application of counter irritants. A chronic form of inflammation may be turned into an acute form by the application of counter irritants. Based on intensity of local irritation, counter irritants are classified into different categories:

A) **Rubefacients**: Cause mild irritation and congestion (redness) in the local skin area: Liniment of turpentine, ammonia or camphor; Iodine ointment with methyl salicylate.
B) **Vesicants**: Cause localized vesicles or blisters by severe irritation and damage to the capillaries. Vesicles appear due to accumulation of serous exudate in the superficial skin layers: Ointment of red iodide of mercury (10%); Ointment containing 7% of red iodide of mercury and 7% cantharadin.
C) **Pustulants**: Cause severe inflammation, even of deep-seated cutaneous tissues, and causes pustules (blisters filled with pus due to destruction of cells): Strong ointment of red iodide of mercury (25%); Cantharidin ointment (12%)

**10. Wound Healers:** These are drugs capable of facilitating or enhancing the processes of wound healing (burns or ulcers) by preventing secondary bacterial infections through antiseptic action: Zinc oxide (as 20% ointment or 10% aqueous solution), povidone iodine ointment (1%), chlorhexidine (1% solution), Lugol's iodine solution, nitrofurazone ointment (0.2%), chlorehexylenol (dettol), chlorhexidine (savlon) etc.

## EXERCISE

1. **Write a short note on the following**:
   a) Emollients b) Astringents c) Antipruritics d) Counter irritants

2. **Define the following and give one example for each**:
   a) Keratolytics b) Emollients c) Antipruritics d) Astringents
   e) Counter irritants f) Rubefacients g) Wound healers h) Vesicants
   i) Caustics j) Escharotics k) Keratoplastics

3. **Matching** (Parallel pairs) or **Multiple choices** (Right choices):
   a) Emollient: Olive oil/Wool fat/Bees wax/Soft or hard paraffin/Vaseline/Glycerine/Glycerol
   b) Demulcent: Glycyrrhiza/Methyl cellulose/Glycerine/Propylene glycol
   c) Astringent: White lotion/$ZnSO_4$ solution/ZnO ointment/Calamine lotion
   d) Adsorbents: Bentonite/Calamine/Boric acid/Starch/Mg.stearate/Zn stearate/ZnO
   e) Antipruritics: Boric acid/Calamine/Zn carbonate/$ZnSO_4$/White lotion/Antibacterial ointment
   f) Keratolytics: Silver nitrate/Antimony trichloride/Salicylic acid/$CuSO_4$

4. **Give the composition of the following**:
   a) Calamine lotion b) Astringent paste c) Caustic solution
   d) Solution for hyperkeratosis e) Eye drops in kerato conjunctivitis

5. **What treatment you suggest for the following indications**:
   a) Limb sprain in a horse b) Yoke tumor in a bullock c) Hyperkeratosis in a cow
   d) Dermatitis in a dog/buffalo e) Eczema in a dog f) Horn bud removal in a calf
   g) Pruritis in a horse h) Granulation growth on skin of a calf

6. **Give the most appropriate reason in one or two sentences for each of the following statements**:
   a) Corticosteroids/Antihistamines/Antibiotics/Antifungals are included in antipruritic ointments.
   b) Ointments with antiseptics promote superficial wound healing.
   c) Counter irritants promote healing process.
   d) Counter irritants are used in chronic inflammation

# Chapter – 28: VITAMIN PHARMACOLOGY

Vitamin has its origin from vital + amine, though all the amines are not amines. Vitamins are the essential organic nutrients present in minute quantities in a variety of foods. Adequate daily intake of all the vitamins must be ensured in all the species of animals and birds. Vitamins have diverse actions in the body and their deficient intake leads to diseases (avitaminosis or deficiency). Ruminal and intestinal microflora synthesize B-complex vitamins. Antibiotic therapy, especially the broad spectrum ones, by oral dosing result in destruction of beneficial microflora. Vitamins are categorized as i) Fat soluble vitamins (A, D, E and K) and ii) Water soluble vitamins (B-Complex Vitamins and vitamin C).

## 1. Therapy of Fat Soluble Vitamin Deficiency

| Vitamin | Deficiency Sign/Symptom | Treatment |
|---|---|---|
| A | Keratinization of epithelial surfaces, night blindness, low sperm quality, fetal resorption, nutritional roup, low egg production/poor egg hatchability | Farm Animals: 100-200 units/kg/day (1-2 gm/day)<br>Poultry: 0.07-0.22 gm/kg feed |
| D | Rickets in young ones and osteomalacia in adults | Farm Animals: 50-100 IU/kg/day; Dog: 200-400 IU/kg/day; Chicks: 150-300 IU/kg/day for about a week in feed |
| E | Muscular dystrophy in young animals. White muscle disease or stiff lamb disease in sheep | All Young Stock: 40 mg/kg/day orally; 25 mg/kg SC or IM; Orally: Swine: 500 mg; Dog: 30 mg/kg/; Poultry: 350 mg/bird/day |
| K | Delayed blood clotting. Spontaneous haemorrhages<br>(Poultry most sensitive) | Menaphtone/menadione: Warfarin Poisoning: All Species: 5 mg/kg IM; Sweet Clover Poisoning: All Species: 1.1 mg/kg IM; Deficiency: Small animals: 2-10 mg/day orally; Large Animals:100-400 mg/day orally;Poultry:1-2 gm/ton of feed |

## 2. Therapy of Water Soluble Vitamin Deficiency

| Vitamin | Deficiency Sign/Symptom | Treatment |
|---|---|---|
| $B_1$ Thiamine Anurine | Nervous signs, vomiting and diarrhoea. Bracken fern poisoning (Antithiamine) | Horse/Ox:100-1000 mg<br>Calf: 5-50 mg; Sheep: 20-200; Pig: 5-100 mg; Cat: 1-20 mg; Dog: 5-50 mg: SC, IM or orally |
| $B_2$ Riboflavin | Curltoe paralysis in chicks. Anaemia, dermatitis and scours in calves. Slow growth, low fertility, eye discharges, irritation, photophobia in horse/pig | Horse: 40 mg daily in feed<br>Pig: 5 mg orally |
| $B_6$ Pyridoxin | Acrodynia (dermatitis, hyperkeratinization and acanthosis of skin) in dogs. Degeneration of spinal and demeylination of peripheral nerves | Same as for thiamine |
| Nicotinic Acid/Niacin | Pellagra, black tongue or brown mouth in dog. Rough scaly skin, oral and GI ulceration and diarrhoea in pig, perosis, dermatitis and inflammation of tongue in chicks.<br>(Pellagra Preventing Factor) | Calf: 25 mg/day SC<br>Pig: 01-0.3 gm SC or 0.2-0.9 gm orally<br>Dog: 5-10 mg/kg IM<br>Cat: 10-30 mg/kg IM |
| $B_{12}$ Hydroxy-cobalamin | Bush sickness, nakuruitis or grand taverse disease in ruminants. Hind limb weakness, inco-ordination, hair or wool loss, stunted growth etc in all animals (Anti- Pernicious Anaemia Factor) | Dog & Cat: 2-4 microgram/ kg/day IM |
| H Biotin, Coenzyme R | Fatty liver and kidney syndrome in broiler chicken fed entirely on wheat ration. Egg white contains antibiotin avidin. | 100 microgram/chick/day orally |

| | | |
|---|---|---|
| Choline | Perosis (slipped tendon in poultry). Fatty liver and ataxia in dogs, cats and Pigs | Dog: 550 mg/kg/day orally<br>Cat: 25-50 mg/day orally or SC<br>In milk fever or ketosis in cattle/buffaloes |
| C Ascorbic Acid | No definite signs can be attributed | Horse: 2-4 gm SC; Bull: 1-2 gm SC every 3-4 days up to 6 weeks;<br>Cow: 1-2 gm IV and 2 gm SC before mating or 2 gm SC once or twice a week up to 6 doses; Dog: 25-75 mg/day orally SC |

**Vitamin Toxicity:** Vitamin A toxicity is called as hypervitaminosis A, the signs of which include lethargy, colic, alaopecia, dry scaly skin (hyperkeratosis), restlessness, brittle hooves and nails and accelerated ESR. The signs of hypervitaminosis D are decrease in bone mineralization, hypercalcaemia and calcification of soft tissues.

## EXERCISE

1. **Write a short note on** a) Fat soluble vitamins b) Water soluble vitamins

2. **Give the line of treatment of the following**:
   a) Night blidness in a dog
   b) Nutritional roup in poultry
   c) Rickets in a pup
   d) Stff lamb disease/WMD in sheep
   e) Spontaneous haemorrhages in poultry
   f) Curltoe paralysis in chickens
   g) Acrodynia/Acanthosis/hyperkeratosis in a dog
   h) Perosis/Slipped tendon in poultry
   i) Bush sickness in ruminants
   j) Osteomalacia in a dog
   k) Sweet clover hay poisoning in cattle
   l) Bracken fern poisoning in cattle
   m) Pellagra in a dog
   n) Nakuritis/grand taverse disease in cattle

3. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
   a) Vitamin A: Night blindness/Hyper keratinization/Low semen quality/Fetal resorption/Nutritional roup
   b) Vitamin D: Rickets/Osteomalacia
   c) Vitamn E: Muscular dystrophy/WM disease in sheep/Stiff lamb disease
   d) Vitamin K: Delayed blood clotting/Spontaneous hemorrhages
   e) Vitamin $B_1$: Thiamine/Anurine/Nervousness/Bracken fern poisoning
   f) Ribiflavin: Vitamin $B_2$/Curltoe paralysis/dermatitis in calves/Photophobia in horse
   g) Pyridoxin: Vitamin $B_6$/Acrodynia in dog/Hperkeratinization in dog/Acanthosis of skin in dog
   h) Niacin: Vitamin $B_3$/Pellagra preventing factor/Black tongue in dog/Brown mouth in dog/Rough scaly skin in pig/Perosis in chicks
   i) Hydroxycobalamin: $B_{12}$/Anti-perniciuos anaemia factor/Bush sickness/Nakuruitis/Wool loss
   j) Vitamin H: Biotin/Coenzyme R/Fatty liver in chicken/Avidin
   k) Choline: Perosis
   l) Vitamin A toxicity: Hyperkeratosis/Alopecia/Dry scaly skin/Brittle hooves and nails/Increased ESR
   m) Vitamin D toxicity: Demineralization of bones/Calcification of soft tissues/Hypercalcaemia

4. **Substantiate the following statements by giving the most appropriate reason in one or two sentences:**
   a) B-complex vitamin supplementation not usually required in ruminants.
   b) Ruminants orally treated with broad spectrum antibiotics need vitamin B-complex supplementation.
   c) Thiamine is given in bracken fern toxicity in horses.
   d) Vitamin K is to be administered in warfarin/Sweet clover poisoning/Coumarol toxicity.
   e) Excess vitamin D intake results in calcification of soft tissues.

# Chapter – 29: ENDOCRINE PHARMACOLOGY

Anterior pituitary, the master gland, under the control of hypothalamus, secretes a number of hormones, which not only acting on several target tissues, but also controlling the function of other glands, is responsible for the physiological performance of the animal. Hypothalamus (rightly credited as 'pharmacological museum') forms and secretes a number of hormones (formerly called as releasing factors) which regulate the endocrine function of anterior pituitary. Hypothalamus in turn is under the control of higher centres of brain. There exists a functional-balancing coordination between the hormones of peripheral glands-anterior pituitary hormones and hypothalamus in maintaining physiological homeostasis.

The peptidergic neurons, which secrete the releasing hormones, are under the central neuronal control, through pathways that release dopamine, NorA, 5-HT and opioid peptides. Dopamine release from tuberohypophyseal dopaminergic neurons, through portal circulation, also reaches anterior pituitary.

## 1. Hypothalamic Hormones and Agonists/Antagonists

**Somatorelin (GHRH)** regulates release of somatotrphin (GH) from anterior pituitary. **Sermorelin**, an analogue of somatorelin is used to test the GH (somatotrophin) secretion.

**Somatostatin** inhibits release of GH and TSH from anterior pituitary, insulin and glucagon from pancreas. **Octreotide**, an analogue of hypothalamic somatostatin, acts like somatostatin. It is used in treating carcinoid tumors, glucagonomas and pituitary adenomas, and acromegaly (hypersecretion of GH in adults).

**Thyrotrophin releasing hormone (TRH)** regulates release of TSH (thyrotrophin) from anterior pituitary. **Protirelin**, a synthetic TSH analogue, is used for diagnosis of thyroid disorders.

**Corticotrophin releasing hormone (CRH)** regulates release of corticotrophin (ACTH) and beta-endorphin from anterior pituitary. CRH release is inhibited by **Glucocorticoids.**

**Gonadoreophin releasing hormone (GnRH)** releases follicular stimulating hormone (FSH) and luteinizing hormone (LH) or interstitial cell stimulating hormone (ICSH) from anterior pituitary.
**GnRH agonists:** Synthetics: Gonadorelin, buserelin, leuprorelin, goserelin and nafarelin.
**GnRH releasers:** Clomiphene, an oestrogen antagonist stimulates GnRH release.
**GnRH antagonist:** Danazol acts by inhibiting release of GnRH.

## 2. Anterior Pituitary Hormones and Agonists/Antagonists

**Somatotrophin:** Secretion is regulated by GHRH, modulated by somatostatin. Deficiency results in **dwarfism**, can be treated by recombinant-somatotrophin. Excess results in **gigantism** in young ones and **acromegaly** in adults, which can be controlled to some extent by dopamine agonist bromocriptine and somatostain analogue octreotide.
**Prolactin:** Control function of mammary gland and milk production. A **dopamine agonist** bromocriptine antagonizes prolactin by decreasing its secretion, can be used to terminate or prevent lactation or galactorrhoea due to its excess secretion (in women). **Dopamine ($D_2$) antagonists** (chlorpromazine, haloperidol, sulpiride, thioridazine, clozapine etc) stimulate prolactin release.
**Follicular Stimulating Hormone (FSH) and Luteinizing Hormone (LH): In Females:** By acting on ovaries these hormones stimulate follicular development (ripening of graffian follicle). FSH stimulates oestrogen release. LH stimulates ovulation and later regulates progesterone secretion from CL.
**In Males: FSH** maintains the integrity of seminiferous tubules and spermatogenesis through an action on Sertoli cells. The **ICSH** (LH) stimulates Leydig cells to secrete testosterone.

**Corticotrophin (ACTH):** Controls synthesis and release of adrenal glucocosteroids (mineralocorticoid synthesis and release by renin-angiotenin system). Tetracosactide, a synthetic analogue of human ACTH is used in human medicine.

## 3. Posterior Pituitary Hormones and Agonists/Antagonists

**Antidiuretic Hormone (ADH):** Regulates water metaolism of the body through its action on distal tubule and collecting tubular epithelium of nephron causing reabsorption of most of the water passing through the nephron. Its mode of action is activation of adenyl cyclase, increase in formation of cAMP and phosphorylation of channels promoting water reabsorption. Absence or deficiency of ADH causes diabetes insipidus (water loss due to excretion of large volumes of dilute urine) Antagonism of its action results in diuresis. NSAIDs and carbamazepine increase ADH effects. Lithium, colchicines and *Vinca* alkaloids decrease ADH effects (antagonism at microtubules in interfering with movement of water in channels). ADH is also called as **vasopressin** (powerful vasoconstriction in skin, and of coelic, mesenteric and coronary vessels).

Synthetic analogs of ADH/vasopressin are desmopressin (DDAVP: 1-deamino-8-D-arginine-vasopression), lypressin, terlipressin and felypressin used in the treatment of diabetes insipidus. Desmopressin has lesser vasoconstrictor effect than vasopressin; whereas lypressin has no vasoactivity. Felypression is used as a vasoconstrictor with local anaesthetics. Demeclocycline (a tetracycline) also induces diuresis by inhibiting the action of ADH in DCTs and collecting duct.

The pharmacology of oxytocin is discussed under oxytocics.

## 4. Adrenal Cortisteroids

These mainly constitute glucocorticoids (hydrocortisone and corticosterone) and mineralcorticoid – aldosterone, and to some extent testosterone. Excess and deficiency of glucocorticosteroid formation and /or release cause Cushing's syndrome and Addison's disease, respectively. The effects of glucocorticoids include:

**A. Metabolic Effects:**

a) **Carbohydrate Metabolism:** Reduction in cellular uptake and utilization of blood glucose and increase in gluconeogenesis causing hyperglycaemia. Hyperglycaemia induces insulin secretion promoting glycogen storage in liver.

b) **Protein Metabolism:** Reduction in protein synthesis and increased protein catabolism in muscles

c) **Fat Metabolism:** Permissive effect in conjunction with epinephrine, which causes activation of lipase through increase in cAMP formation and its subsequent activation of cAMP-dependent kinase. Glucocorticoids are essential for synthesis of this kinase. Excess secretion or administration for long term causes redistribution of body's fat as seen in Cushing's syndrome.

**B. Inflammatory and Immune Responses:** Glucocortioids exert antiinflammatory and immunosuppressive effects, which are generally regarded as pharmacological effects of glucocorticoids, and shared by of NSAIDs (See under Analgesics-Antipyretics-Antiinflammatory agents). These effects are due to formation and release of an array of mediators. These effects may also be credited to physiological role of glucocorticoids, checking the 'overshoot' of body's powerful defense mechanisms.

a) Reduction in formation of mediators such as prostaglandins, leukotrienes, PAF, interlukins, tumor necrosis factor, cell adhesion factor, plasma complement components, NO and IgG due to suppression of specific genes transcription. Also suppress histamine release from basophils.

b) Inhibition of vasodilatation and formation of oedema, inhibition of neutrophil migration and macrophage function, proliferation and action of T helper cells, suppressed fibroblast function, reduced production of collagen and glycosamonoglycans (reduced progress of chronic inflammation or healing and repair). Tendency for development of osteoporosis may also occur due to suppressed action of osteoblasts and increased action of osteoclasts.

The above effects are due to interaction of glucorticoids with intracellular steroid receptors and modification of gene transcription, inducing synthesis or suppression of synthesis of specific proteins (enzymes).

The biosynthesis of glucocorticoids is inhibited by metyrapone, which can be used as a diagnostic test to assess ACTH secretion. Aminoglutethimide and ketoconazole (antifungal agent) also inhibit steroidogenesis. These drugs can be used in traeating Cushing's syndrome.

**Principles of Corticosteroid Therapy:**

1. Dosage schedule must be according to individual cases and should meet the requirement of replacement to the physiological levels. Higher doses result in atrophy of adrenal cortex and permanent hypofunction of the gland. When prolonged therapy is required, small doses are selected. Therapy must also be withdrawn gradually.
2. Corticosteroids do not cure the disease (inflammation), but give relief due to antiinflammatory effects.
3. Use should be avoided during active infections, unless compulsory. If used, the microbes may spread over extensive areas (inhibition of natural tissue barrier processes). Use in microbial diseases must be accompanied by high doses of antibiotics.
4. For chronic affections, especially, joint pains, conjunctivitis, dermatitis, pruritis etc, local application should be preferred (systemic use may cause other effects and atrophy of the gland).
5. Should not be used simultaneously with immunization/vaccination schedules.
6. Use is contraindicated in diabetes mellitus, hypertension, renal sufficiency, late pregnancy (late pregnancy), corneal ulcers and hepatic insufficiency.

**Clinical Uses of Corticosteroids:**

Dogs: Arthritis, asthma, eczema, dermatitis, pruritis, conjunctivitis and iridocylitis or acute anterior uveitis (increased proliferation of cells and protein in anterior chamber of eye, causing low intraocular pressure, conjunctiva hyperaemia, iridal swelling, photophobia etc).
Horse: Lameness, conjunctivitis, iridocyclitis.
Cattle: Lameness, mastitis and ketosis.
Synthetic corticoids can be used in large animals to induce parturition (Cow: 10-30 mg/kg IM, induces parturition within 72 hr). The glucocorticoids of clinical importance are cortisone, hydrocortisone and synthetic corticoids like, prednisone, prednisolone, dexamethasone, betamethasone etc. Exogenous administration of corticosteroids is better than administration of ACTH, which may not release required levels of glucocorticoids.

**Doses and Administration of corticosteroids:**

Cortisone and hydrocortisone: Horse and Cattle: 800-1500 mg daily IM; Dog: 2 mg/kg IM.
Prednisone and prednisolone: Horse and Cattle: 100-250 mg daily IM; Dog: 0.5-2 mg/kg IM.
Dexamethasone: Cattle: 5-20 mg daily IM; Horse: 2-5 mg daily IM; Dog: 0.1-1 mg daily IM.
The above (except dexamethasone) are injected @ 50-200 mg into bursa, tendon sheath or joint capsule in lameness in cattle or horses

**Mineralocorticoid:** Aldosterone increases Na+ reabsorption and increases K+ and H+ efflux into lumen of renal tubule. Mineralocorticoid deficiency is treated by replacement therapy with fludrocortisone. The action and antagonists of **aldosterone** are discussed under angiotensins and diuretics.

## 5. Thyroid Hormone and Antithyroid Drugs

The thyroid hormones are thyroxine ($T_4$) and triiodothyronine ($T_3$), whose biosynthesis and secretion is under the control of TSH/thyrotrophin. $T_4$ is more than $T_3$. Thyroid hormones stimulate metabolism, increasing metabolic rate accompanied by increased oxygen consumption, and also influence growth and development in general.

**Hypothyroidism:** It is due to under function of thyroid activity, severe thyroid insufficiency results in myxoedema. Thyroid insufficiency lowers libido in males and causes anoestrus in females.
Deficiency can be corrected by administration of thyroxin orally @ 5 microgram/kg 2 or 3 times/day in dogs and 50-100 mg/day in cattle.

**Hyperthryroidisn (thyrotoxicosis)** is of two types: Diffuse toxic goitre (also called as Grave's disease or exophthalmic goitre) and toxic nodular goitre, which can be treated by administration of antithyroid drugs (or surgically):

**Antithyroid Drugs**
These do not cure the disease, but help in controlling the clinical manifestations. The antithyroid drugs either by inhibiting synthesis or interfering with release of thyroid hormones.
**Classification:**

A. **Thioureylenes:** Carbimazole, mehiamazole, thiouracil, methylthiouracil and propylthiouracil: Reduce synthesis of thyroid hormones in the gland by inhibiting
   a) Thyroperoxidae catalysed oxidation reactions
   b) Iodination of tyrosyl residues in thyroglobulin.
   c) Formation of peroxidase-iodide complex.
   d) Coupling of iodotyrosyl residues.
   e) Impairment of conversion of $T_3$ to $T_4$ thyroid follicles.
   All the above actions are as consequence of competitive inhibition of thyroperoxidase.
   Carbimazole is a prodrug converted to methimazole. Both the drugs cross placenta and are also excreted through milk.
   Methylthiouracil: 30-60 mg/kg/day; Thiouracil: 10-15 mg/kg/day; Propylthiouracil: 10 mg/kg/day orally.
B. **Inorganic Ions:** Perchlorate and thiocynate: Compete with iodide for the iodide transport system in the membrane of the follicle cell (competitive inhibition) of iodide uptake.
   Cabbage and raw soybeans also exert antithyroid effect by preventing iodide uptake. *Brassica* plant species also contain a goitrogen.
C. **Iodide:** Excess iodide in circulation following high oral doses, blocks the release of preformed thyroid hormones in the gland. The hormones remain within the gland itself- thyroid constipation. Excess iodide in diet may also inhibit iodination of thyroglobulin by preventing $H_2O_2$ generation.
D. **Iodne $^{131}$:** The radioactive iodine is taken up and processed by the gland in the same as the normal (stable) iodide, finally getting incorporated into thyroglobulin. The beta and gamma radiation emitted by iodine $^{131}$ exerts cytotoxic action, selectively destroy or decays the thyroid follicle cells.
   Na/K Iodide: 2-5 mg/kg.

Several other drugs exert antithyroid effect, as a side effect. Such drugs are not called as antithyroid drugs, which include NSAIDs, corticosteroids, beta-adrenoceptor blocker propranolol, hypoglycaemic sulfonylureas, phenothiazine tranquilizers and antidepressant lithium carbonate

## 6. Paratharmone and Calcitonin

The calcium/bone metabolism is regulated by paratharmone (chief cells of parathyroid gland), calcitonin (C cells of thyroid) and vitamin D. Paratharmone secretion is stimulated by hypocalcemia and inhibited by hepercalcemia. The secretion of calcitonin is stimulated by hypercalcemia and inhibited by hypocalcemia.
Vitamin D is necessary for absorption of calcium and phosphorus from intestines.
Paratharmone increases blood calcium levels by and by increasing calcitriol synhesis. Calcitriol increases plasma calcium by calcium mobilization from bone, increasing intestinal absorption and decreasing renal excretion of calcium. Calcitonin reduces calcium resorption from bone by inhibiting osteoclast activity.
Paratharmone promotes bone formation by stimulating osteoblast activity and can be used to treat osteoporosis. Vitamin D2 is available as ergocalciferol, alfacalcidol and calcitriol.

Paratharmone is under development as recombinant PTH
Calcitonin as Salcatonin (synthetic salman calcitonin) and porcine calcitonin
A physiological inhibitor of bone resorption is osteoprotegerin, which can also be used in osteoporosis.
Thiazide diureticsalso exert some antiresorption effect on bones.

## 7. Insulin and Oral Hypoglycaemic Drugs

**Insulin** is a peptide hormone secreted by the endocrine part of pancreas, the beta-islets of Langerhans. Its physiological role is in glucose homeostasis. Insulin release is increased by GIT hormones gastrin, secretin and cholecystokinin; gastric inhibitory polypeptide, glucagon like polypeptide, amino acids (arginine and leucine), fatty acids, and pharmacologically through stimulation of parasympathetic nervous system and oral hypoglycaemic sulfonylureas. Insluin secretion is lowered by somatostatin, galanin (an endogenous ATP-sensitive potassium channel activator) and amylin, and pharmacologically by sympathetic system. Epinephrine increases blood glucose by inhibiting insulin secretion through $\alpha_2$-adrenoceptor activation in β-islet cell membrane and promoting glycogenolysis through activation of $\beta_2$-adrenoceptors in skeletal muscles and liver.
Insulin action is to facilitate utilization of glucose by the cells. On activation of cell membrane insulin-receptor by insulin, a specific insulin-linked carrier protein transports glucose into the cell for utilization within the cell. Insulin deficiency causes diabetes mellitus characterized by hyperglycaemia. In man, the disease is of two types: Non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM) or juvenile diabetes. The disease can be induced by alloxan and streptozotocin which selectively destroy the beta-islets of pancreas impairing insulin synthesis or pancreatectomy.
Treatment of Diabetes Mellitus:

A. **Insulin Preparations:** Many types are available for human use. These are administered parenterally and ineffective orally:
   a) Conventional insulin preparations of bovine origin: Plain insulin, protamine zinc insulin (PZI), insulin zinc suspension-amorphous (semi lente), isophane (NPH), insulin zinc suspension (lente) and insulin zinc suspension-crystalline (ultra lente).
   b) Purified Porcine and Human Insulins: Actrapid, rapidica, huminsulin, insulatard, mixtard, lentard, zinulin
B. **Oral Hypoglycaemics:** These drugs lower blood glucose level and are effective after oral administration.
   **a) Biguanides:** Metformin and phenformin: These do not cause insulin secretion. Presence of endogenous or exogenous insulin is necessary for their action. Their hypoglycaemic action is due to several mechanisms:
      i) Inhibition of gluconeogenesis in liver.
      ii) Increased peripheral utilization of glucose due to aerobic glycolysis.
      iii) Increasing sensitivity of tissues to insulin.
      iv) Delayed absorption of glucose from intestines.

   In addition, biguanides also lower serum LDL and VLDL levels.
   **b) Sulfonylureas (SUs):**
   **First Generation SUs**: Tolbutamide, chlorpropoamide and tolazamide
   **Second Generation SUs**: Glyburide, glibenclamide and glipizide.
   The FGSUs are more potent and long acting (high plasma protein binding) than SGSUs
   Their mode of action is stimulation of secretion of insulin by blocking of ATP-sensitive K+ channel receptors on pancreatic beta cells. The blockade results in lowered K+ conductance, membrane depolarization, stimulation of Ca++ influx and release of insulin.These also inhibit gluconeogenesis in liver.
   **c) Sulfonylurea Like Acting:** Repaglinide and nateglinide. These are not related chemically to sulfonylureas, but act in similar fashion stimulation of insulin secretion from beta-cells.

**d) PPARγ receptor agonists:** Thiazolidinediones: Rosiglitazone and pioglitazone. The PPARγ (peroxisome proliferator-activated receptor-gamma) receptors (nuclear) which are present in adipose tissue, muscle and liver is complexed with $R_{XR}$ (retinoid X receptor). These drugs make the complex to bind with DNA triggering gene transcription of insulin and several other proteins. Thus these drugs acting as nuclear PPARγ receptors promote insulin synthesis. These drugs may also lower insulin resistance in muscle and adipose tissues; thus reducing insulin requirement in these tissues.

**e) Alpha-Glucosidase Inhibitors:** Acarbose: Inhibition of the enzyme in intestines delays the breakdown of complex carbohydrates and their absorption. Thus, the postprandial increase in blood glucose is prevented, reducing the requirement of insulin.

**Drug Interactions:** Phenylbutazone, salicylates, bishydroxycoumarin, alcohol, MAO inhibitors and sulfonamides potentiate hypoglycaemic effect of sulfonylureas; whereas, thiazide diuretics, corticosteroids, chloramphenicol, furosemide and oral contraceptives reduce sulfonylurea-induced hypoglycaemia.
Diabetes mellitus is also considered as one of the common hormonal disorders in dogs and cats, where ultralente insulin @ 0.5 microgram/kg and 1-3 micrograms, respectively, once or twice in a day parenterally can be used. Subsequent dose schedules are to be adjusted monitoring blood glucose levels. Oral hypoglycaemic glipizide is also recommended in cats @ 2.5 mg orally, twice a day. The drug is contraindicated in dogs.

## 8. Glucagon

A peptide hormone formed in alpha cells of endocrine pancreas. It is credited as the "fuel generating' or 'fuel mobilizing' hormone. It increases blood glucose levels by enhancing glycogenolysis, proteolysis, lipolysis and gluconeogenesis. Its secretion is related to blood glucose and fatty acid levels: increased when their levels are low and decreased when their levels are high. Sympathetic and parasympathetic nerve activities also increase its secretion, but somatostatin inhibits its secretion. It has both positive inotropic and chronotropic effects on heart. Glucagon has important clinical use in reversing cardiac failure due to over dosage of beta-adrenoceptor antagonists and overcome hypoglycaemia in unconscious human subjects. It may be useful in treatment of circulatory shock @ 50 microgram/kg IV.

## 9. Somatostatin

It is also a peptide hormone of pancreatic origin, from the delta-cells, lie adjacent to alpha cells. It is similar to the GHIH of hypothalamus. In exerts inhibition of insulin and glucagon release within the pancreatic islets. **Octreotide** is a synthetic analogue of somatostatin.

## 10. Amylin

A peptide hormone found in secretary granules, along with insulin, in beta cells of pancreas. It inhibits insulin secretion, but also cosecreted. Its physiological role in glucose metabolism is not understood.

## 11 Female Sex Hormones: Agonists and Antagonists

**Oestogens:**

**A. Natural:** Oestradiol, oestrone and oestriol. Oestradiol is the most potent and main oestrogen of ovary.
**B. Synthetic Steroids:** Diethylstilbestrol, mestranol, oestrol, ethinyloestradiol, dienoestrol, etc.
**C. Synthetic Nonsteroidal Compounds:** Hexastrol and chlorotrianisene.

Natural oestrogens are mainly synthesized in ovary and placenta, and in minute levels in testis and adrenal cortex. The mode of action of oestrogens involves activation of intracellular receptors (ERα and ERβ) triggering specific gene transcription in target organs in consonance with their biological effects. Oestrogens are responsible for development of secondary sexual characteristics and control of proliferative phase of endometrium.
Oestrogens are primarily used clinically for reversal of ovarian failure for maintenance of normal integrity of female reproductive tract and mammary gland (anatomical, structural and functional).

**Tamoxife** a partial **agonist-antagonist of oestrogens** with antioestrogenic effect on mammary tissue, but has oestrogenic effect on plasma lipids, myometrium and bone. It is used in treatment of breast cancer and for antiosteroporotic action in women.

**Clomiphene, raloxifene and cyclofenil (antioestrogens)** through inhibition of oestrogen binding in anterior pituitary (prevention of oestrogen negative feedback) cause increased release of GnRH and gonadotrophins resulting in stimulation of oestrogen secretion and proliferation of ovaries and induction of ovulation (may be used clinically).

**Progestogens:**

**A. Natural:** Progesterone and hydroxyprogesterone.

**B. Synthetic:** Megestrol, mibolerone, melengestrol, medroxyprogesterone and proligestone.

The testosterone derivatives ethisterone, norethisterone, norgestrl, ethynodiol, allyloestrenol and dimethiesterone have progesterone-like activity and can be used orally.

The natural progestogen is progesterone, which is mainly synthesized in CL and placenta and in minute levels in testis and adrenal cortex. Main functions of progesterone include making the endometrium ready for implantation of fertilized ovum (to establish pregnancy) and subsequently (from placenta) maintenance of pregnancy/gestation and stimulation of development of secretary alveoli in mammary gland.

The mode of action of progestogens involves activation of intracellular receptors, like other steroid hormones, triggering specific gene transcription in target organs in consonance with their biological effects.

Oestrogen stimulates progestogen receptor density; whereas, excess progesterone inhibits progestogen receptors.

**Mifepristone**, an antiprogestogen (partial agonist on progestogen receptors) along with $PGF_{2\alpha}$ can be used to terminate early pregnancy. As it also inhibits ovulation (in late follicular phase of the cycle) can be used as a post-coital contraceptive in women.

## 12. Male Sex Hormones (Androgens): Agonists and Antagonists

Testosterone is the natural androgen, mainly synthesized in interstitial cells of testes and in very small amounts in adrenal cortex (in both the sexes) and ovary in females.

Testosterone is responsible for growth and development of secondary sex organs, secondary sex characters in males and characteristic male bahaviour. It is also essential for spermatogenesis and maintaining libido in males. The androgen exerts anabolic effects (nitrogen retention, protein sparing electrolyte retention, stimulation of erythropoiesis, increases muscle mass and enhances bone growth).

In peripheral target cells the effects are due to testosterone along with its active metabolite dihydroxytestosterone. In anterior pituitary, only testosterone exerts control in secretion of LH/ICSH. The mode of action of testosterone or dihroxytestosterone is activation of intracellular steroid receptors, similar to other steroid hormones.

Androgens are clinically used for testicular failure and as anabolic agents.

**Testosterone Preparations:**

**Testosterone Esters: Parenteral use**: Testosterone propionate/phenylpropionate/cypionate/ enanthate.

**Oral use:** Methyl testosterone, fluoxymesterone, mesterolone and testosterone undecanoate.

**Transdermal:** Testderm patch and androgel for rubbing to the scrotal skin (human use).

Synthetic derivatives of testosterone including boldenone undecylenate, nandrolone decanoate and stanozolol are used as **anabolic** steroids.

Oestrogens (inhibiting gonadotrophin secretion) and progestogens (competitive antagonism at intracellular receptors) possess antiandrogen activity.

**Cyproterone** (a derivative of progesterone) is a partial agonist-antagonist at dihydrotestosterone receptors in target cells. It inhibits pituitary synthesis of gonadotrophins. It is used to treat masculinizsation in women and depress libido in men (sexual offenders).

**Flutamide** (nonsteroidal antiadrogen) along with GnRH to treat prostrate cancer in man.
**Finasteride** prevents conversion of testosterone to dihydroxytestosterone by inhibiting 5α-reductase. Since the androgen metabolite has greater affinity than testosterone for androgen receptors in prostrate, finasteride is more beneficial than testosterone in treating prostrate cancer. This therapeutic manipulation is synergistic when finasteride is coupled with $\alpha_1$-adrenoceptor antagonists.

## 13. Reproduction Therapy in Animals

| Hormone | Clinical use | Species: Dose and Administration |
|---|---|---|
| GnRH | Cystic ovaries | Cow: 0.1 mg/day IM or IV |
| TSH | Acathosis nigricans | Dog: 1-2 U/day IM for five days |
| LH / ICSH | a. Follicle stimulation<br>b. Ovulation<br>c. Cystic ovaries<br>d. Testosterone Production | Cattle/Horse: 25 mg<br>Sheep: 5 mg<br>Swine: 2.5 mg<br>Dog: 1 mg<br>IV, repeat after 1-4 weeks |
| FSH | Folluculogenesis and superovulation | Cow: 5 mg at 12 hr for a total dose of 40 mg IM on cycle days 0-14 + 40 mg $PGF_{2\alpha}$ IM 48 hr after first FSH injection |
| HCG | a. Stimulation of ovary<br>b. Cystic ovaries<br>c. Cryptorchidism<br>d. IC stimulation | Cattle/Mare: 1000-2000 U IV, 10,000 U IM<br>Sheep: 400-800 U IV<br>Swine: 500-1000 U IV<br>Dog/Cat: 100-500 U IV |
| Testosterone Propionate (in oil) | a. Sterility<br>b. Hypogonadism<br>c. Reduced libido<br>d. Aspermia | Bull/Stallion: 100-300 mg<br>Ram: 20-25 mg<br>Dog: 5-20 mg SC<br>SC or IM for three days |
| DES | a. Misalliance.<br>b. Urine incontinence<br>c. Anal oedema<br>d. Prost. hypertrophy | Dog: 1 mg/kg IM within 7 days of mating.<br>Dog: 0.5-1 mg/kg/day orally or IM for 7 days or more |
| Mestranol | Misalliance | Dog: 5 mg/kg orally on 5$^{th}$ day of mating (No conception) |
| Estradiol | Uterine atony/abortifacient (early pregnancy) | Cow/Mare: 10-20 mg IM one injection |
| Progesterone (in oil) | Prevention of embryonic death | Cow/Mare: 50-100 mg; Ewe: 10-15 mg; Swine: 15-25 mg; Dog/cat: 2.5-5 mg IM daily for 7-14 days. |
| Megestrol | Oestrus suppression | Dog: 2.2 mg/kg IM for 8 days during prooestrus or 0.6 mg/kg IM for 30 days during anoestrus |
| Melengestrol | Increase wt. gain/feed efficiency & to suppress oestrus | Feedlot Heifers: 0.2-0.5 mg/day orally. Withdraw two days before slaughter |
| PMSG | a. Induction of oestrus<br>b. Follicle stimulation<br>c. Ovulation | Cow/Mare: 1000-2000 U SC, IM or IV<br>Ewe: 100-500 U; Sow: 200-800 U SC, IM or IV<br>Dog/Cat: 25-200 U SC, IM or IV |
| PMSG | Superovulation | Cow: 1500 U IM or 15$^{th}$ or 16$^{th}$ day of oestrus; Ewe: 700-1400 U IM on any day from 4-13 days of oestrus; Goat: 1000-1500 U IM on days 16,17 or 18 oestrus |
| PMSG + $PGF_{2\alpha}$ | Superovulation | Cow:PMSG 2000 U IM on any day from 9-13 days of oestrus, followed by 25-30 mg of $PGF_{2\alpha}$ IM (40-48 hr) |
| $PGF_{2\alpha}$ | Synchronization of oestrus | Cow: 25-30 mg IM on any day of oestrus from 5 to 16 days or 30 mg IM twice with a 10 day gap. Ewe/Dow: 10-15 mg IM on any day from 5 and 14 days of oestrus |

## EXERCISE

1. What are coticosteroids? Describe their metabolic and pharmacological effects and discuss the principles of corticosteroid therapy.
2. **Write a short note on the following**:
   a) Pharmacological effects of glucocorticoids
   b) Principles of corticosteroid therapy
   c) Oral hypoglycaemics
   d) Antithyroid drugs
   e) Insulin
   f) Androgens
   g) Oestrogens
   h) Progestogens
   i) Clinical value of glucocorticoids
   j) Prostaglandins in reproduction
   k) Inflammatory and immune responses of corticosteroids
3. **Differentiate between the following**:
   a) Glucocorticoid and mineralocorticoid
   b) Biguanides and sulfonylureas
   c) Insulin and glucagon
   d) Diabetes mellitus and diabetes insipidus
   e) Gigantism and acromegaly
4. **What hormone therapy you suggest for the following conditions**? Give its dose and route of administration:
   a) Chronic joint pain/lameness in a bullock
   b) Cystic ovary in a cow
   c) To induce ovulation in a cow/mare/ewe
   d) Reduce libido in a bull/stallion
   e) Growth promotion in a dog/foal
   f) Misalliance in a bitch
   g) Oestrus suppression in a bitch
   h) Superovulation in cow
   i) Synchronization of oestrus in cows
   j) Sterility/Hypolibido in a bull/stallion
5. **Write the mode of action of the following**:
   a) Oestrogens
   b) Andrgens
   c) Progestogens
   d) Sulfonylureas
   e) Biguanides
   f) Methimazole
   g) Thiouracil
   h) Perchlorate
   i) Calcitonin
   j) Paratharmone
   k) Insulin
   l) Cortisone
   m) Aldosterone
   n) Vasopressin
   o) Acarbose
   p) Sulfonylureas
6. **What is the source of the following**:
   a) Insulin
   b) Glucagon
   c) Amylin
   d) Somatostatin
   e) Calcitonin
   f) Paratharmone
   g) FSH
   h) LH/ICSH
   i) Vasopressin
   j) ADH
7. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
   a) Sermorelin: Somatorelin analog/Used to test GH secretion
   b) Somatostatin inhibits secretion of: GH/TSH/Insulin and glucagon
   c) GnRH analog: Gonadorelin/Buserelin/Nafrelin/Leuprorelin/Goserelin
   d) Cloimphene: Releases GnRH/Oestrogen antagonist
   e) Bromocriptine: Prolactin anatoginist/Dopamine agonist/Used in galactorrhoea
   f) Stimulate prolactin release: Chlopromazine/Haloperidol/Sulpiride/Clozapine/Dopamine antagonists
   g) ADH analog: Desmopressin/Terlipressin/Felypressin
   h) Inhibitor of steroidogenesis: Metyrapone/Aminoglutethimide/Ketoconazole/To treat Cushing's disease
   i) Aldosterone antagonist: Spironolactone/Eplerenone/Canrenone
   j) Antithyroid: Carbimazole/Thiouracil/ Perchlorate/Thiocyanate/*Brassica* spp./Cabbage/Raw soybeans
   k) Antithyroid side effect: NSAIDs/Propranolol/Sulfonylureas/Phenothiazines/Lithium carbonate
   l) Beta islet damage/Diabetic inducer: Alloxan/Streptozotocin
   m) Sulfonylurea: Chlopropamide/Glibenclamide/Glipizide/Tolbutamide
   n) Sulfonylurea like: Repaglinide/Nateglinide
   o) PPAR-gamma agoniststs: Rosiglitazone/Pioglitazone/Promote insulin synthesis
   p) Potentiation of sulfonylurea hypoglycaemia: Phenylbutazone/Sulfonamides/Salicylates/MAO inhibitors
   q) Alpha-Glucosidase inhibitor: Acarbose/Delays CHO absorption/Lowers post meal hyperglycemia
   r) Reduce sulfonylurea hypoglycemia: Thiazide diuretics/Corticosteroids/Chloramphenicol/Furosemide
   s) Natural oestrogen: Oestradiol/Oestrone/Oestriol
   t) Natural progestogen: Progesterone/Hydroxyprogesterone
   u) Synthetic steroidal oestrogen: DES/Mestranol/Oestrol/Dienostrol/Ethinyloestradiol
   v) Synthetic nonsteroidal oestrogen: Hexastrol/Chlorotriansene
   w) Synthetic progestogens: Megestrol/Milbolerone/Melengestrol/Proligestone
   x) Oestrogen receptors: $ER_{alpha}$/$ER_{beta}$/Nuclear/Trigger gene transcription
   y) Parenteral testosterone: Testosterone propionate/Testosterone cycpionate/Testosterone enanthate
   z) Oral testosterone: Methyl testosterone/Fluoxymesterone/Mesterolone/Testosterone undecanoate
   aa) Cyproterone: Agonist-antagonist of dihydrotestosterone receptors
   bb) Flutamide: Nonsteroidal androgen/Prostrate cancer
   cc) Finasteride: Inhibits 5-alpha reductase
   dd) Cystic ovaries: GnRH/LH/ICSH/HCG
   ee) TSH: Acanthosis nigricans
   ff) Oestradiol: Uterine atony
   gg) Super ovulation: FSH/PMSG
   hh) Misalliance: Mestranol/DES
   ii) Cryptorchidism: HCG
   jj) Oestrus inducer: PMSG
   kk) Hypercalcemia: Calcitonin
   ll) Hypocalcemia: Paratharmone
   mm) Calcitonin: Inhibition of osteoclasts

nn) Paratharmone: Inhibition of osteoblasts
oo) Salcatonin: Synthetic salmon calcitonin
pp) $PGF_{2alpha}$: Oestrus synchronization
qq) Protirelin: TSH analog
rr) Mifepristone: Antiprogestone
ss) Tamoxifen: Oestrogen agonist-antagonist.
tt) Raloxifene: Oestrogen antagonist
uu) Main oestrogen: Oestradiol
vv) Amylin: Inhibits insulin secretion
ww) Biguanide: Metformin/Phenformin
xx) Tetracosactide: ACTH analog
yy) Mineralocorticoid: Fludrocortisone
zz) Glucocorticoid: Prednisone
aaa) Octreotide: Somatostatin analog
bbb) Antioestrogen: Clomiphene/Cyclofenil
ccc) GnRH antagonis: Danazol
ddd) Megestrol/Melegestrol: Oestrus suppression
eee) Vitamnin D2: Ca mobilization from bones/Increased Ca abosorption from intestines/Decreasing renal excretion of Ca
fff) Physiological inibitor of bone resorption: Osteoprotegerin
ggg) Osteoporosis: Osteoprotegerin/Paratharmone (low levels)
hhh) Vitamin D2: Calcitriol/Ergocalciferol/Alfacalciferol
iii) Diabetes insipidus: DDAVP/Desmopression/Terlipression/Felypressin
jjj) Antagonism of ADH: Lithium/Colchice/*Vinca* alkaloids
kkk) Acarbose: Alpha-glucosidase inhibitor
lll) Propylthiouracil: Thyroid peroxidase inhibition

8. **Give the most appropriate reason for each of the following statements in one or two sentences**:

a) Glucocorticoids have a rôle in body's defense mechanisms.
b) Glucorticoids are also used in allergy.
c) Glucorticoids can induce osteoporosis.
d) Insulin is called fuel burning hormone.
e) Glucagon is useful in circulatory shock.
f) Androgens can be used in debility.
g) ADH is also called vasopressin.
n) Finasteride is used to treat prostrate cancer.
p) Corticosteroids should be avoided in infections.
q) Raw cabbage/soybean causes hypothyroidism.
h) Alloxan/Streptozotocin induces diabetes.
i) Metformin is ineffective in IDDM.
j) Tamoxifen is used in breast cancer.
k) Clomiphene/Cyclofenil induces ovulation.
l) Mifepristone is post-coital contraceptive.
m) Cyproterone is used in sexual offenders.
o) Water loss occurs in diabetes insipidus.
r) Glucagon is called fuel generator/mobilizer.
s) Hypothalamus is 'pharmacological museum'.
t) Rosiglitazone/Pioglitazone/$PPAR_{gamma}$ receptor agonists promote insulin synthesis.
u) Metyrapone/Ketoconazole is used in Cushing's syndrome.
v) Corticosteroid supplementation should be similar to their physiological levels.
w) Corticosteroid therapy and immunization should not go simultaneously or hand in hand.
x) Corticosteroids are contraindicated in diabetes/renal insufficiency/late pregnancy.
y) Glucocorticoids exert permissive effect with adrenaline in causing hyperlipemia.
z) Felypression is used with local anaesthetics.
aa) Though desmopressin/Lypressin is an analog of vasopressin, their effects are not identical to those of vasopressin.
bb) Demeclocycline induces diuresis.
cc) Acarbose reduces the post-prandiol blood glucose level in diabetics.
dd) Troglitozone treatment is beneficial in diabetics.

# Chapter 30: PRODUCTION PHARMACOLOGY

## 1. Growth Promoters

These are agents added to the animal feeds (feed supplements) in order to enhance the feed conversion efficieny in terms of increased formation of muscles, fat and bones (body growth), especially in feed-lot animals, including poultry.

A. **Steroid Hormone Growth Promoters (SHGPs)**: Oestradiol and testosterone:
Oestradiol acts through stimulation of production of GH and insulin-like growth factor -1 (IGF-1); increases both muscle mass and fat. Testosterone promotes muscle mass by stimulating protein synthesis (aminoacid incorporation). Progesterone suppresses oestrus and promotes growth.
Dosage: SC pellet implantation: Oestradiol 20 mg with 200 mg progesterone or testosterone (effective for three to four months). Adding testosterone or progesterone to oestradiol helps in slow release of oestradiol (prolongation of effect).
Synthetic Steroids: Trenbolone acetate (TBA, 140, 200 or 300 mg pellet implants)) and melengestrol acetate (MGA, in feed 0.25-0.5 mg/heifer daily). Implants containing 140 mg TBA with 20 mg oestradiol are also used.
Synthetic Nonsteroidal Oestrogens: Zeranol (@ 35 mg in small cattle and 12 mg in sheep as SC implant, effective for up to four months; a synthetic analogue of oestrogenic toxin zearalenone). Diethylstilbestrol (DES) and hexestrol are not to be used due to residue problem (banned in many countries).
The SHGPs should not be used in breeding stock (exert negative feed back on pituitary leading to reduced secretion of LH and FSH (delayed puberty/oestrus, reduced conception and retarded testicular development). TBA should not be given to preganant heifers (masculinization of female fetus and risk of dystokia).

B. **Growth Hormne**: A peptide hormone not to be used orally. It is ineffective in poultry. A recombinant GH is available. It promotes milk production (up to 20%).

C. **Beta-Adrenoceptor Agonists**: $Beta_2$ agonists (Clenbuterol): Muscles and fat cells are rich in these receptors; whose activation promotes muscle formation and prevents muscle breakdown at the cost of adipose tissue ($beta_3$). Not clinically used in food animals due to severe side effects and adverse meat quality.

D. **Antimicrobial Growth Promoters**: Used in adult ruminants.
**Ionophore Antibiotics**: Monensin, lasalocid, salinomycin and maduramicin: They act through beneficial alteration of ruminal microflora and proportion of volatile fatty acid production (decrease acetate and methane production and increase propionate production: enhanced feed conversion efficiency). Help in dry matter digestibility and in improving nitrogen utilization. These are added @ 5-30 ppm levels in ration.
**Nonionophore Antibiotics**: Bambermycins, virginiamycin and zinc bacitracin. Help in improving the health (check low level infections) and production of livesock through beneficial alteration of ruminal/intestinal microflora; used in ruminants and poultry. These exert nitrogen-sparing action, making available more aminoacids for protein synthesis. Their extensive use as feed supplements is discouraged due to risk of emergence of bacterial resistance to antibiotics.

E. **Microbial Growth Promoters**: Probiotics: *Lactobacilli, Streptococci* or yeasts: Aid in establishing beneficial intestinal microbial population (promoting fermentation in formation of lactate and checking multiplication of pathogenic bacteria: improve digestion and thus feed efficiency).

## 2. Anabolic Steroids

These are synthetic derivatives of androgen testosterone, but different fom the androgen in that these have more of anabolic actions and less of androgenic effect. These steroids act through stimulation of nuclear recptors, triggering specific enzyme formaton causing enhanced synthesis of muscle proteins (myosin, myofibrils, sarcoplasm, enzymes etc). Also exert positive nitrogen balance (reduced nitrogen elimination and antagonism of catabolic effect of glucocorticoids), enhance erythropoiesis, promte appetite and increase weight gain. Anabolic therapy has to be supported by adequate nutrition (protein and calories). The side effects of anabolic steroids include increased libido, testicular atrophy, azospermia in males; anoestrus and clitorial atrophy, masculinization in females; retention of sodium and water and hepatotoxicity. The clinical uses of anabolic steroids include promotion of weight gain in weak and debilitated animals, convalescing animals (disease/surgery). Anabolic steroids should not be used in feed-lot animals (residue problem).

Alkylated Anabolic Steroids:

Oxymetholone: Dog & Cat 2-5 mg/kg/day orally

Stanozolol: Dog: 2-4 mg twice a day orally or 20-40 mg once in a week deep IM; in cats half of dog's dose; Horse: 0.5 mg/kg deep IM once in a week for four weeks.

Nonalkylated Anabolic Steriords:

Nandrolone decanoate: Dog & Cat: 1 mg/kg IM once in a week; Horse: 1 mg/kg IM once in 3-4 weeks.

Boldenone undecylenate: Horse 1 mg/kg IM every three wees.

## 3. Therapy of Milk Fever

This metabolic disease occurs in high-yielding lactating cows due to impairment of calcium homeostasis; characterized by hypocalcemia (excessive drain in milk, impaired absorption from intestines, under mobilization from bones: inadequate paratharmone and 1, 25-dihydroxyvitamin D). Treatment consists of:

Calcium borogluconate (25% solution) @ 150-250 mg/kg slow IV

## 4. Therapy of Ketosis

The disease is also called acetonemia in cattle and pregnancy toxema in sheep. Occurs due to impairment of energy metabolism characterized by hypoglycemia, ketonema and ketonuria; occurs in high-yielding lactating animals in pregnancy-lactation cycle (post-parturient period). Treatment comprises of:

Cattle: Glucose (50% solution) @ 200-225 gm twice during first two days followed by 100-110 gm once a day for two days + 10 mg dexamethasone or 5 mg flumethasone. Oral feeding of 110-200 gm of sodium propionate. Protamine zinc insulin @ 200-300 IU SC once on alternate days.

Sheep: Oral administration (drenching) of 150 ml of a solution containing 45 gm glucose, 8.5 gm sodium chloride and 6.17 gm glycine and electrolytes.

## 5. Therapy of Post-Parturient Haemoglobinuria

The disease occurs in high-yielding cows/buffaloes after parturition due to phosphorus deficiency (hypophosphatemia), characterized by hemoglobinuria. Hypophosphatemia leads to impaired glycolysis in erythrocytes causing low ATP formation, which in turn disrupts the structural integrity of erythrocytes resulting in hemolysis. Cu or Se deficiency aggravates the disease. Treatment comprises of:

Blood transfusion (about 4-5 lires in an adult cow/buffalo. A 300 ml of water solution containing 60 gm of sodium acid phosphate. Oral feeding of 100-120 gm bone meal or equivalent dicalcium phosphate and administration of hematinics.

## EXERCISE

1. **Write short notes on the following**:
   a) Growth promotants
   b) Hormonal growth promoters/Feed additives
   c) Nonhormonal growth promoters/Feed additives
   d) Antimcobial growth promoters/Feed additives
   e) Anabolic steroids

2. **Give the line of treatment of the following conditions**:
   a) Ketosis in a cow
   b) Milkfever in a cow
   c) Post-parturient hemglobinuria in a cow
   d) Growth stimulant during convalescence (disease/surgery)
   e) Growth promotion in broilers/feed-lot cattle

3. **What do you mean by the follwing?/(Define)**:
   a) Growth promoter b) Probiotic c) Inonophore d) Anabolic

4. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
a) Oestradiol/Testosterone: Natural steroidal hormone growth promoter
b) Trenbolone/Melengestrol: Synthetic steroid hormone growth promoter
c) Zeranol/DES: Synthetic nonsteroidal hormone growth promoter
d) Clenbuterol: Beta-adrenoceptor growth promoter
e) Growth homone: Recombinant growth promoter
f) Antimcrobial growth promoters: Monensin/Salinomycin/Maduramicin/Bambermycins/Virginamycin/Bacitracin
g) Ionophore growth promter: Salinomycin/Lasalocid/Monensin/Maduramicin
h) Nonionophore growth promter: Bambermycins/Virginiamycin/Zinc bacitracin
i) Probiotic: Microbial growth promoter/Lactobacilli/Some strains of Streptococci
j) Synthetic anabolics: Oxymetholone/Stanozolol/Nandrolone decanoate/Boldenone undecylenate
k) Oxymetholone/Stanozolol: Alkylated anabolic steroids
l) Nandrolone decanoate/Boldenone undecylenate: Nonalkylated anabolic steroids
m) Milk fever: Ca borogluconate
n) Ketosis: Glucose/glucocorticoids/Dexamethasone/Flumethasone/Sodium propionate/Protamine zinc insulin
o) Post-parturient haemoglobinuria: Hypophosphatemia/Erythrolysis/Na acid phosphate/Dicalcium phosphate
p) Zeranol: Analog of oestrogenic toxin/Synthetic nonsteroidal growth promoter

5. **Give the most important reason for each of the follwing statements**:
a) Improved feed conversion efficiency is the basis of growth promotant supplementation.
b) Oestrodial promotes growth.
c) Testosterone promotes growth.
d) DES/Hexestrol should not be used as growth promotants in food producing animals.
e) Steroid hormone growth promotants should not be used in breeding stock.
f) $Beta_2$ adrenoceptors though promote growth. are not generally used in food animals.
g) Ionophores promote growth in ruminans.
h) Certain antibiotics are used as feed supplemens in food producing animals.
i) Nonionophore antibiotic feed supplementation as growth promotant is discouraged.
j) Ionophore antibiotics as growth promotants alter proportion of volatile faty acid synthesis in ruminants.
k) Probiotics exert growth promotant action in ruminants.
l) Testosterone, in general, is not recommended as an anabolic.
m) Synthetic analogs of testosterone are used as anabolic steroids.
n) Anabolic steroids act as growth promotants.
o) Anabolic steroids should not be used in feed-lot animals.
p) Anabolic steroid therapy should have concurrent adequate nutrition of the animal.
q) Ca borogluconate should be given in cows with milk fever.
r) Treatment of ketotic cows consists of administration of glucose and glucocorticoids.
s) Sodium acid phosphate is given to cows/buffaloes with post-parturien hemoglobinuria.
t) Hemolysis occurs in post parturient hemoglobinuria.
u) Ketonemia develops in ketosis.
v) Anabolic steroid therapy is done through SC implants.
w) TBA is added to oestrodial implants in anabolic therapy.

# Chapter – 31: IMMUNOPHARMACOLOGY AND BIOENHANCERS

Immunopharmacology deals with the therapeutic effects of drugs/chemicals on immune responses of man and animals. Immunotoxicology deals with the undesirable effects of chemicals on immune system of man and animals. Immune responses are important defense mechanisms for the host animals. Their impairment will results in increase incidence of infection and thus may indirectly influence the survival of the individual or the species.

**Types of Immune Responses**: The immune responses fall into two major types based on resistance against the antigenic invaders.

**1. Humoral immune response:** Primarily directed against the extracellular or exogenous invaders (bacteria, many protozoa and helminhs). The invaders are destroyed by production of antigen specific antibodies by B-lymphocytes. This type of immune response is called the humoral immune response, since antibodies are found in the body fluids (humours). This antibody associated immune response is mediated by B-lymphocytes.

**2. Cell-mediated immune response:** It is directed against the intracellular or endogenous invaders (virus, intracellular bacteria or protozoa, cancer cells) which cause cellular abnormalities and these abnormal cells are destroyed by specialized cytotoxic cells. This immune response is mediated by T-lymphocytes which are thymus dependent and can be abolished by thymic irradiation or neonatal thymectomy. The cellular immune responses are totally absent in athymic animals (nude mice). Although the two types are quite different, the different types of cells cooperate with each other (T-cells are important in influencing the ultimate expression of humoral immunity).

**Generation of Humoral and Cellular Immune Resposes**

**1. Humoral immune response:** The antigen (Ag) is processed by macrophages or other antigen processing cells (APC). In the next step, APC coupled with class II major histocompatibility complex (MHC) is presented to the CD4 helper T-cells which are activated by interleukin-1 (IL-1; produced by macrophages). Activated helper T-cells proliferate and secrete cytokines and these in turn augment proliferation and differentiation of antigen activated B-cells into antibody (Ab) secreting plasma cells. Antibody secreted by plasma cells finally binds and inactivate the antigen.

**2. Cell-mediated immune response:** The foreign antigen is processed and presented to CD4 helper T-cells. The activated T- helper cells liberate IL-2 and other cytokines that in turn promote the proliferation and maturation of precursor cytotoxic lymphocytes (CTL) that have been activated by antigen presented with MHC class I molecule. Mature CTL (killer cells) recognize cells carrying the antigen and destroy them.

**Immunomodulation** refers to pharmacological manipulation of the immune system and it may involve an increase in the magnitude of immune response or suppression of unwanted immune response. Both the processes together are termed immunomodulation and the drugs are immunomodulators.

**1. Immunosuppressants**

The drugs which inhibit cellular/humoral or both the immune responses are called immunosuppressants. The primary immune responses can be more effectively suppressed than the secondary immune responses and therefore, immunosuppressive therapy must be started before, rather than after exposure to the immunogen.

The clinical indications of immunosuppressive therapy are

i) In organ transplantation, to prevent the rejection of foreign tissue/organ
ii) For prevention of Rh haemolytic disease of new born in human
iii) For the treatment of autoimmune disorders when immune system is sensitized by endogenous proteins that are recognized as foreign antigen.

The immunosuppressive agents can be classified as follows:

1. **Specific T- cell inhibitors**: Cyclosporine (a polypeptide obtained from a fungus *Tolypocladium inflatum* Gams) and Tacrolimus (a macrolide antibiotic obtained from *Streptomyces tsukubaensis*); these selectively inhibit T-lymphocytes and CMI. They interfere with antigen-stimulated activation

and proliferation of helper T cells, as well as expression of IL-2 and other cytokines. These are administered orally or IV for organ transplantation: Cyclosporine @ 10 mg/kg every day or on alternate days; Tacrolimus @ 25-50 µg/kg/day. Both are highly toxic to kidney, liver and bone marrow.

2. **Cytotoxic drugs**: Cyclophosphamide, azathioprine, chlorambucil and mycophenolate, mofetil: These act by blocking proliferation and maturation/differentiation of T and B lymphocytes; many of the cytotoxic anticancer drugs have immunosuppressant action.
3. **Corticosteroids**: Prednisolone: Used alone or in combination with other immunosuppressants; these bind with intracellular protein receptors and inhibit T cell proliferation, T cell-dependent immunity and expression of genes encoding cytokine synthesis. Used in treating immune-mediated skin diseases/dermatoses in man and animals and neoplasia in man.
4. **Antibodies**:
    a) Antithymocyte globulin (ATG): A purified immunoglobulin prepared from hyper immune serum of horse, rabbit, sheep or goat, following immunization with human thymic lymphocytes; binds to the surface of T lymphocytes and impair their function. Used in organ transplantation.
    b) Muromonab CD3 monoclonal antibody: Its binding with CD3 glycoprotein on T lymphocytes blocks access of antigen to its recognition complex. Produces quick effects and hence used in acute rejection of organ transplants.
    c) Rho(D) immunoglobulin: Consists of a human IgG globulin containing high titre of antibodies against the Rh (D) antigen on RBC; blocks formation of primary antibody in response to a foreign antigen, if passively administered at the time of initial exposure to the antigen. It is used in Rh negative mothers to prevent sensitization to Rh (D) antigen, which on rechallenges lead to erythrobalstosis fetalis or hemolytic disease of newborn.

**2. Immunostimulants**

These agents increase the host resistance to disease by stimulating the cellular or humoral immunity. They need not to be administered together with antigen to stimulate immunity. They are clinically used in the treatment of immunodeficiency diseases (AIDs in human), chronic infectious diseases and cancer. Their most common uses are in chronic skin diseases of dog (chronic recurrent Staphylococcal pyoderma), equine sarcoids, bovine papilloma, equine respiratory diseases, certain tumors of dog and cat and immunosuppressive viral diseases. The immunostimulants are:

a. **Vitamins A, E and C**: Vitamin A is required for maintaining cellularity of lymphoid organs. It stimulates the production of IL-2 by lymphocytes and IL-1 by macrophages. Vitamin A deficiency in pigs results in decrease in **resistance**. Vitamin E enhances cellular and humoral immunity. Vitamin C regulates antigen clearance, interferon production and lymphocyte proliferation. Dietary addition of Vitamin C augments immunity.
b. **Minerals**: Selenium is a part of glutathione-peroxidase enzyme, and is an antioxidant. It protects neutrophils from oxidatative damage and improves humoral immunity. Zinc stabilizes membrane structure and reduces oxidative cellular damage. Its deficiency leads to atrophy of thymus and lymphoid tissues. Copper is needed for microbicidal action of peripheral leucocytes. Cobalt is essential for maintaining neutrophil function.
c. **Thymic Hormones**: Thymosin and thymopoitin contribute to maintenance and balance of immunity; stimulate immunity in animals. Thymosin stimulates maturation of T cells. Thympoitin improves neutrophil and macrophage function.
d. **Cytokines**: These are a group of diverse proteins (interlukins, interferons, TNF, colony-stimulating factor) produced by leucocytes and related cells; regulate and coordinate immune response by inter cellular communication and improve natural defense mechanism. IL-2 and Interferons are most commonly used as therapeutic immunostimulants. Interferons produce antiviral, antitumor, antiparasitic and immunomodulatory effects. Interferons can be used in bovine respiratory disease, bovine mastitis, canine retroviral infection and in treating leukaemia, renal carcinoma, genital warts, chronic hepatitis B infection in man. The **cytokine inducers**:

i. Regression V: An emulsion of Mycobacterial cell fraction; used in mammary tumors and mammary adenocarcinoma in dogs and sarcoids in horses.
ii. Acemannan: A polysaccharide derived from *Aloe vera* plant; activates macrophages and releases IL-1, IL-6, TNF and NO from macrophages leading to tumor apoptosis.

e. **Immunoglobulins**: It consists of pooled human/animal plasma obtained from donor/slaughtered animals; contains all of the immunoglobulins. The antibodies present in this fraction are given to passively immunized deficient patient IM or IV. It is used in immunodeficient diseases, hematological disorders (autoimmune hemolytic anaemia) and infectious diseases in man (measles and hepatitis).

f. **Microbial Products**: These include
i. BCG: Consists of a muramyl peptide; producing generalized immunostimulation on both T and B cells.
ii. Staphage lysate: A preparation of *Staph. aureus* and polyvalent Staphylococcal bacteriophage; used in combination with antibiotics @ 1 ml SC once in a week, for treatment of superficial Staphylococcal pyoderma in dog. It stimulates T cells and activates phagocytes.
iii. *Staph. aureus* Bacterin-Toxoid: Used in prevention of Staphylococcal mastitis in cattle and canine bacterial hypersensitivity @ 0.1 ml/day intradermally, initially for five days followed by at weekly intervals for a month and then at monthly intervals.
iv. Propioni bacterium acenes bacterin: Contains a muramyl dipeptide; used in dog @ 0.25-2 ml IV, once or twice in a week; also for treating recurrent respiratory disease in horse, bovine pipilloma and pyoderma in dog.

g. **Synthetic Compounds**:
i. Levamisole: Stimulates CMI; used in treatment of rheumatoid arthritis and colorectal cancer in man. Also reduces incidence of bovine mastitis, endometritis and fetal death.
ii. Isoprinosine: Possesses antiviral property (interferon production). It increases antiviral activity of natural killer cells, T cells and monocytes. Used in treating AIDs in man and New Castle disease and influenza in birds.
iii. Polyribo nucleotides: Include polyribo-inasinic acid (Poly-I) and polyribocytidylic acid (Poly-C); stimulate macrophages and T cells, and induce release of T-helper lymphokines, colony stimulating factor, interferon production. Useful in treating canine viral hepatitis.

## 3. Bioenhancers

A biohancer may be defined as a substance that can increase the efficacy of conventional drugs like chemotherapeuticals (anticancer drugs, antibiotics, antiviral drugs etc). The exact mode of action of bioenhancers is still under investigative stage; however a bioenhancer is suggested to act through improving the bioavailability of the drug, potentiating the drug molecule through conformational changes and making the target cells more receptive to the drug, "without itself acting as a drug". The bioenhancers when administered after mixing with a drug enhance the effectiveness of the drug, without altering action or property of the drug. Bioenhancers may also act through "molecular synergism" with the drug. The "combo-therapy" (drug with enhancer) helps in reduction in dosage and associated toxicity of the drug and minimise the emergence of drug-fastness or resistance among the pathogens. At present bioenhancers are envisaged to be beneficial as adjuncts to chemotherapy. These may also be called as drug facilitators. Taking leads from the anicient Indiam system of medicine Ayurveda, the Indian medicinal plants offer invaluable resource material for bioenhancer molecules, which can help in alleviating the diseases like cancer, AIDS and other immunodeficiency states, osteoporosis, arthritis, Alzheimer and Parkinson's diseases, obesity etc. The vegetable bioenhancers may not replace the conventional allopathetic drugs, but can be of synergistic adjuncts to them. Many compounds of vegetable origin are on R and D priorities of pharmaceuticals. Natural products are anticipated to rule the therapeutic world and the biopharmaceuticals shall be the remedies of the near future. The examples of bioenhancers in final stages of premarket investigation include:

a) **Distillate of cow urine**: The ancient treatises of Indian system of medicine recognized cow urine ("*Go Mutra*") to possess innumerable curative potentials. A distillate of cow urine, labeled as a bioenhancer, has been credited to enhance the activity of rifampin (anti-TB antibiotic) by about 5-7 folds against *E. coli* and 3-11 folds against Gram negative bacteria. It is also found to enhance potency of anticancer drug taxol against a human breast cancer cell line in *in vitro* assays. Both the findings were granted US patent.
b) **Pepperine**: It is obtained from black pepper, a patent has also been obtained for its bioenhancer action by CSIR. Pepperine has been found to increase the efficacy of anti-TB drugs, halving their dosage. It is in final phases of drug development.
c) **Curcumin**: It is from Turmeric (haldi): Rhizomes of *Curcuma longa*. It has wound healing, anti-inflammatory, anti-cancer and immunostimulant properties. It may also have bioenhancer potential. The US patent obtained for its wound healing and other medicinal was got cancelled by the Govt. of India (CSIR).
There are many other **likely** bioenhancer candidates detected in Indian medicinal plants. These are reported to possess one or more of the actions such as antistress, antiulcer, antidiabetic, antioxidant, immunostimulant, rejuvenating or antiaging, cardiotonic, hepatotonic, nerve tonic or brain tonic, memory enhancing, radioprotection etc. Several of the medicinal herbs also have bioactive principles which augment tissue homeostasis and/or improve organ function helping in alleviating the disease state.
The following Indian medicinal plants possess compounds, which may be the future bioenhancers:

*Abelmoschus esculentus*
*Abutilon indicum*
*Acanthopanax senticosus*
*Acorus calamus*
*Aegle marmeloes*
*Allium sativum*
*Aloe vera*
*Alstonia scholaris*
*Asparagus adescendens*
*Asparagus racemosus*
*Astercantha longifolia*
*Azadirachta indica*
*Bacopa monnieri*
*Beta vulgaris*
*Celastrus paniculatus*
*Centella asiatica*
*Citrus aurantium*
*Cumis sativus*
*Diospyros malabarica*
*Diospros melanoxylon*
*Eclipta alba*
*Emblica officinalis*
*Glycerrhiza glabra*
*Holarrhena antidysenterica*
*Lawsonia inermis*
*Leptidenia reticulata*
*Mangifera indica*
*Mentha piperata*
*Mentha spicata*
*Moringa oleifera*
*Mucuna prurita*
*Musa paradisiaca*
*Myristica fragrans*
*Ocimum sanctum*
*Phyllanhus amarus*
*Phyllanthus emblica*
*Piper betle*
*Podophyllum hexandrum*
*Prus amygdalus*
*Psidium guajava*
*Punica granatum*
*Rubia cordifolia*
*Solanum trilobatum*
*Syzygium cumini*
*Terminalia arjuna*
*Terminalia chebula*
*Tinospora cordifolia*
*Typha elephantia*
*Trichosanthes cucumeria*
*Wedila calendulacea*
*Withania somnifera*
*Xanthium strumarium*
*Zingiber officinale*

## EXERCISE

1. What is immunomodulation? Classify the drugs altering immune function with suitable examples and discuss their clinical application.

2. **Write a short note on the following**:
   a) Immunostimulants b) Immunosuprressants c) Bioenhancers

3. **Differentiate between the following**:
   a) Immunostimulant and immunosuppressant b) Drug and bioenhancer
   b) Humoral immunity and CMI

4. **What do you mean by the following? Answer in one or two sentences for each**:
   a) Cow urine distillate b) Curcumin c) Pepperin d) Immunoglobulins
   d) Thymic hormones e) Cytokines

5. **Matching** (Parallel pairs)
   a) Cyclosporine: Specific T-cell inhibitor/Macrolide antibiotic/Immunosuppressant
   b) Immunosuppresant: Cyclophosphamide/Azathioprine/Chlorambucil/Mycophenolate/Mofetil
   c) Immnostimulant: Vitamins A. E and C/Se/Zn/Cu/Thymosin/Thymopoitin/Cytokines
   d) Cytokine inducers: Regression V/Acemannan (*Aloe vera*)
   e) Synhetic immunostimulants: Levamisole/Isoprinosine/Pol-I/Poly-C

6. **Give the most appropriate reason of each of the following statements**:
   a) Immunosuppressants are used in organ transplant patients.
   b) Cow urine distillate acts as bioenhancer.
   c) Pepperine is regarded as a bioenhancer.
   d) A bioenhancer is not called a drug.
   e) Bioenhancers can be used as adjunct to chemotherapy.

# SECTION V: CHEMOTHERAPY

## Chapter – 32: GENERAL CONSIDERATIONS

Chemotherapy is therapy of infectious diseases and malignancy by use of chemicals, called chemotherapeutic agents. It may be defined as the treatment of systemic infection (caused by bacteria, viruses, fungi, protozoa, helminths etc) or malignancy with specific chemicals that have selective toxicity for the infecting organism/malignant cell with no or minimal effects on the host cell. The chemotherapeutic agents have minimal or negligible effect on the host. Due to similarity between the malignant cells and pathogenic microbes, the treatment of neoplastic diseases with drugs is also called chemotherapy. Selective toxicity is an essential property of chemotherapeutics, which selectively target the pathogen. The basis of selective toxicity is variation in structural components and/or metabolic processes between the host cell and the pathogen. Most of the antibiotics exhibit a great degree of selectivity such as:

a. Inhibition of bacterial cell wall formation (penicillins/cephalosporins). Mammalian cells lack cell wall.
b. Inhibition of bacterial protein synthesis (tetracyclines, aminoglycosides etc). Presence of specific binding sites on bacterial ribosomes, but not on mammalian ribosomes.
c. Bacteriostatic effect of sulfonamides is due to PABA antagonism in folic acid synthesis. Mammalian cells do not form folic acid from PABA, but utilize the preformed folic acid.

Antibiotics constitute a large proportion of chemotherapeuticals. The word antibiotic is derived from antibiosis (opposite to symbiosis). An antibiotic may be defined as a chemical substance produced by microorganisms (fungi, actinomycetes or bacteria) that suppresses the growth, multiplication or may eventually kill the other microorganisms, at a very low concentration (antiviral, antibacterial, antifungal or antiprotozoan antibiotics). Antiparasitic drugs are the next most important group of chemotherapeuitic agents. These include drugs used against ectoparasities (ectoparasiticides) and internal parasites (anthelmintics or antiprotozoan drugs). The use of drugs in treatment of malignancies comes under cancer chemotherapy. However, both anticancer and antiviral drugs exert poor selectivity. They may exert similar effects on normal cells as they do in the target diseased cells of the host.

### 1. Historical Background

The ancient Indian system of medicine (Ayurveda) and Chinese medical literature recognized the therapeutic value of soil, plants, minerals and metals in the treatment of infectious diseases like syphilis (with mercury compounds) and malaria (with *Cinchona* bark). Even in the present days of scientific advancement, the rural folklore medicine recommends several age-old remedies in treating carbuncles, boils and many infectious diseases.

The real breakthough in use of synthetic chemicals for killing disease causing organisms came with the discovery of bactericidal and antiparasitic activity of of dyes like methylene blue and arsenicals like arsephenamine by Paul Ehrlich, a German organic chemist in 1890-1910. He coined the term 'chemotherapy' while using arsenical treponemicidal agents, and also introduced the concept of 'chemotherapeutic index', the basis of present day therapeutic index. The works of Ehrlich prompted search for newer chemicals as antibacterials and he was rewarded with Nobel Prize in the year 1909. He is regarded as 'Father of Chemotherapy'. In this direction, another German Gerhard Domagk and his associates (1932-1935) discovered antibacterial activity of another dye (prontosil) which subsequently paved the way for the most popular antibacterials of the modern era, the sulfonamides. Domagk was also honoured with the Nobel Prize in medicine (1938).

Pasteur and Joubert, who showed bactericidal property of common bacteria against Anthrax bacilli, first demonstrated the phenomenon of antibiosis between microorganisms (the basis of antibiotics). The 'golden age' of chemotherapy began in the year 1941 when penicillin was used in treating human bacterial infections. Penicillin was originally a chance/accidental discovery. Alexander Fleming in 1928 working at the Saint Mary's Hospital, London found that contamination of culture plate of staphylococci by spores of

*Penicillium notatum* prevented the growth of the bacteria. He has demonstrated that the mold elaborated a material antagonistic to the growth of staphylococci. He named the substance as penicillin. It was established as an antibiotic by Florey and his associates in treating wounded soldiers during World War II. Fleming, Florey and Chain were awarded Nobel Prize in 1945. The Fleming's discovery paved the way for search of antibacterial agents from several fungi, actinomycetes and bacteria. Streptomycin was isolated from *Streptomyces griseus* by Waksman in 1944. He also tried to explain antibiotic as a chemical substance produced by some microorganisms having inhibiting property on other microorganisms. Subsequently, a host of antibiotics were discovered viz. chloramphenicol in 1947, chlortetracycline in 1948, semisynthetic penicillins since 1958, amphotericin B in 1956, cephalosporins in 1960s, gentamicin in 1964, fluoroquinolones in 1980s and so on. The search continues to find newer antibiotics in place of the older ones to which the pathogens are becoming refractory.

**Antimicrobial agents** (AMAs): Are synthetic as well as naturally obtained (microbial origin) drugs that are used to inhibit or kill microorganisms.

## 2. Classification of AMAs

### A. Based on Antibacterial Action:

**Bacteriostatic**: Suppression of bacterial growth and multiplication: Sulfonamides, tetracyclines, chloramphenicol, erythromycin, linocomycin etc.

**Bactericidal**: Cause death of bacteria: Penicillins, cephalosprins, streptomycin, kanamycin, colistin, bacitracin etc.

### B. Based on Antibacterial Spectrum:

Narrow Spectrum: Effective against a limited group of bacteria:

a) Against Gram positive: Penicillins, erythromycin, lincomycin, bacitracin etc.
b) Against Gram negative: Streptomycin, gentamicin, polymyxin B etc.

Broad Spectrum: Effective against both Gram positive and Gram negative bacteria: Tetracyclines, chloramphenicol, fluoroquinolones, sulfonamides etc.

### C. Based on Mechanisms of Antimicrobial Action:

a. By inhibiting bacterial cell wall formation or causing its breakdown leading to death of the microbes (Penicillins, cephalosporins, bacitracin, cycloserine and vancomycin).
b. By altering microbial cell membrane permeability causing leakage of essential intracellular components: Polyene antifungal antibiotics (nystatin and amphotericin B) exert antifungal action by binding to ergosterol of fungal cell membrane, acting as ionophores cause leakage of cations ($K^+$) from the fungal cell.
c. By inhibiting synthesis of ergosterol in cell membrane of fungi: antifungal drug itraconazole.
d. By disrupting the structural integrity of bacterial cell membrane: The cationic detergent antibiotics polymixin B and colistin interact with bacterial cell membrane and disrupt its structure causing bactericidal effect.
e. By interfering with protein synthesis in bacteria by the following mechanisms:
    a) By altering with the action of tRNA for binding site on 30 S subunit of bacterial ribosome: Tetracyclines.
    b) By forming abonormal codon: anticodon after binding to 30 S subunit of bacterial ribosome causing misreading of message: Aminoglycosides.
    c) By inhibition of transpeptidation after binding to 50 S subunit of bacterial ribosome: Chloramphenicol.
    d) By inhibiting translocation of peptide chain from A site to P site by binding to 50 S subunit of bacterial ribosome: Erythromycin and lincomycin.

f. By interfering with nucleic acid synthesis by the following mechanisms:
   a) By inhibiting nucleic acid synthesis (DNA and RNA): Sulfonamides and sulfones (PABA antagonism), trimethoprim, pyrimethamine and proguanil (inhibition of dihydrofolate reductase).
   b) By altering base-pairing properties of the template: Proflavine and acriflavine cause frameshift mutation altering the codons for synthesis of a new protein instead of the normal protein in bacteria.
   c) Inhibition of either DNA or RNA polymerase in bacteria: Rifamycin and rifampicin (antiTB antibiotics) inhibit bacterial RNA polymerase. Ciprofloxacin and norfloxacin (fluoroquinolones) inhibit DNA gyrase.

**D. Based on sources:**
a. Fungal Origin: Penicillin, Cephalosporin and Griseofulvin.
b. Bacterial Origin: Bacitracin, Polymyxin B, Colistin and tyrothricin.
c. Actinomycetes Origin: Streptomycin, Tetracyclines, Chloramphenicol, Macrolides.

## 3. Principles of Chemotherapy

Successful chemotherapy is based on following principles:

**b.** The basic principle of chemotherapy is the selective toxicity i.e. the drug should selectively inhibit or kill the disease causing pathogenic organism or cancer cells without affecting the host cells.
**c.** Chemotherapy must be rational and needs to be supported by either a clinical or microbiological diagnosis to identify the pathogenic organism(s).
**d.** Characterization of the pathogen(s), including its sensitivity to an AMA is essential.
**e.** Selection of an appropriate drug based on pathogenic organism, patient factors and drug factors. If possible, it is better to use a narrow-spectrum antibiotic, which is more selective and thus cause less interference with the normal resident bacteria.
d. The drug should be used in proper time, by proper route, at appropriate dose rate and for a proper duration. If an antibiotic is used, it is better to administer it as immediate as possible, at a high dose for a short period and continue beyond 48 hr after disappearance of symptoms (unless signs of toxicity are seen). This ensures that the organism is totally eliminated and there is less chance of developing antibiotic resistant bacterial strains. Moreover, the antibacterial activity of a given dose of an antibiotic is inversely proportional to the number of bacteria present. Therefore, earlier the treatment there is more chance that the infecting organism to be caught in their early logarithmic growth phase.
e. Attainment of effective concentration of a chemotherapeutic agent for a sufficient period at the site of infection (tissues or body fluids) is very important.
f. Specific and appropriate supportive therapy should be undertaken to overcome the infection.

## 4. Selection of Antimicrobial Agent

The choice of an AMA in treating an infectious disease is based on the infecting organism, patient and the drug.

**Microorganism related factors:** Successful chemotherapy demands a specific diagnosis, but in field conditions it may not be always possible. In general the choice of AMA is determined by:

A) **Choice based on Clinical diagnosis of an infectious disease**: A preliminary clinical diagnosis should first be made to guess the likely pathogenic organism. In this case, neither the pathogenic organism nor its sensitivity is much variable and therefore clinical diagnosis itself determines the choice of AMA (HS, BQ, Babesiosis in animals and malaria, TB, amoebiasis in humans).
B) **Choice based on microbiological culture and sensitivity test:** In this case, it is neither possible to guess the type of infecting pathogen nor its sensitivity (Osteomyelitis, meningitis, urinary tract infection, wound infection, bronchopneumonia etc). In such cases, isolation, identification and characterization of

the causative pathogen, sensitivity testing and determination of the minimum inhibitory concentration (**MIC**) should be assessed to provide a sound basis for selection of the AMA, as well as its dosage regimen. MIC is the lowest concentration of an AMA that prevents the visible growth and multiplication of a bacterium after 18-24 hr of incubation *in vitro*; MFC is the lowest concentration of an AMA that prevents the visble growth and multiplication of fungus after 18-24 hr of incubation *in vitro*. The minimum antibiotic concentration (**MAC**) is the lowest concentration of the antibiotic at the site of infection that reduces the growth of bacteria i.e. *in vivo* about one-tenth of MIC). The minimum bactericidal concentration (**MBC** is the lowest bactericidal concentration of the antibiotic that results in 99.5% decline in bacterial count *in vitro*). However, under field conditions, it may not be always possible to ascertain the above considerations, and the situation may be as follows:

a) When bacteriological laboratory facility is not available: In such a case, based on experience a broad spectrum AMA (tetracycline, fluoroquinolone, sulfonamides) or combination of antibiotics like penicillin + streptomycin or gentamicin + cephalosporin ± metronidazole (for anaerobic infections) should be administered to cover all likely bacterial pathogens.
b) When bacteriological laboratory facilities are available, but the treatment cannot be delayed: e.g. acute mastitis in cows, septicaemias, meningitis etc, where the specimens should be sent first for microbiological examination and treatment also should be started as in (a). If adequate response is not found, then the AMA is changed later as per bacteriological findings.
c) Bacteriological facility is available and treatment can be delayed for sometimes: e.g. chronic mastitis, chronic urinary tract infection etc. In such situations, it is better to wait for microbiological culture and sensitivity report and then the therapy is started on the basis of microbiological findings.

**Animal Related Factors:**

A) **Age:** Age is one of the important factors determining the pharmacokinetic properties of the drug. Aminoglycosides are excreted slowly in old animals because of poor renal function and therefore full dose of the drug may cause toxicity. Newborns cannot metabolize and excrete chloramphenicol because of deficiency of metabolizing enzyme and cause fatal "Grey Baby Syndrome" (grey discoloration of body, flaccidity of muscles and hypothermia). Tetracyclines are contraindicated in young animals and children as they accumulate in developing teeth and bones (discoloration and weakening).

B) **Functional capacity of kidney and liver:** AMA with low margin of safety must be used very cautiously when the renal and hepatic (organs of disposal) functions are defective. Drugs like cephalothin, cephaloridine, nalidixic acid, tetracyclies, aminoglycosides, amphotericin B etc should not be administered in renal dysfunction. On the contrary, erythromycin, chloramphenicol, rifampin etc should not be administered in liver diseases.

C) **Host defense status**: Integrity of host defense plays an important and critical role in the final eradication of the pathogens, particularly when a bacteriostatic drug is used. Bacteriostatic drugs can cure an infection in a patient with normal defense status (immunocompetent), but bactericidal drugs must be given in a patient with impaired defense. The bacteriostatic drug will be less effective in very young, very old and debilitated animals because of poor or impaired host defense (phagocytosis and immunity).

D) **Pregnancy and lactation**: It is better to avoid all AMAs during pregnancy (particularly during the first trimester period of organogenesis) unless it is very much essential because these may cause abnormality in the fetus (Teratogenecity: Tetracyclines, fluoroquinolones or aminoglycosides). Penicillins, erythromycin and some cephalosporins can safely be given in animals. Nalidixic acid and sulfonamides are excreted through milk and may cause haemolysis in glucose-6-phosphate dehydrogenase deficiency. Chloramphenicol, ivermectin and many other antibiotics and anthelmintics cannot be given to milch animals producing milk for human consumption because of possible human health hazard due to presence of residues in milk.

E) **Drug allergy and idiosyncrasy**: If there is any previous history of allergic reaction of an animal to an AMA, the drug should not be given in that animal. Antibiotics, especially penicillins produce life threatening severe anaphylactic reactions in man and sometimes in animals. Aminoglycosides, erythromycin and sulfonamides, trimethoprim are often associated with allergic reactions and should not be used in allergic patients. Individuals genetically deficient in glucose-6-phosphate dehydrogenase enzyme when treated with primaquine, fluoroquinolones, sulfonamides may suffer from haemolysis.

F) **Presence of blood, pus, CSF and tissue breakdown products** interfere with the efficacy of many AMAs like sulfonamides, nitrofurans and aminoglycoside antibiotics; whereas, these factors do not affect the efficacy of penicillin.

G) **Location of infection** determines the choice of AMA and route of administration. Presence of infection behind the barrier e.g. meningitis, abscess etc.

H) **Effects of AMAs on intestinal microflora**: Ruminants are highly dependent on the integrity of the ruminal microflora and thus oral administration of broad spectrum AMAs (Tetracyclines, chloramphenicol etc.) affects the normal flora and leaving the field free for growth and multiplication of pathogenic yeasts and fungi which results in acute diarrhea.

**Drug Related Factors**:

a) **Sensitivity of the organism to the AMA**: An AMA to which the organism shows highest sensitivity is selected. The sensitivity of a microorganism to different AMA's is determined on the basis of MIC. An organism is considered highly sensitive if the MIC of the AMA is lowest for that organism.

b) **Type of antibacterial activity**: A bacteriacidal AMA is preferred over bacteriostatic in a patient with impaired host defense, in serious life threatening infections and when the infections are behind the barriers.

c) **Antibacterial spectrum**: If the characterization of pathogen is possible then it is far better to use a narrow spectrum AMA which selectively affects the pathogenic organism without much affecting the normal microflora. But when no guess can be made about the nature of organism, usually a broad spectrum AMA is to be used to cover all likely pathogens, but problem of superinfection has to be borne in mind.

d) **Combination of AMAs**: Combination of two bacteriostatic drugs is additive (combinations of tetracyclines, chloramphenicol, erythromycin) or synergistic/potentiation (sulfonamide + trimethoprim). Combination of two bactericidal drugs is also additive, if the organism is sensitive to both (penicillin + streptomycin). But the combination of bactericidal + bacteriostatic are frequently antagonistic (penicillin + tetracycline or chloramphenicol for pneumococci; nalidixic acid + nitrofurantoin for *E. coli*) and hence are not combined. Inhibition of bacterial growth with combination of antibiotics is **antibiotic synergism/potentiation** where their concentration is less than or equal to 25% of the MIC of each antibiotic acting alone. Inhibition of bacterial growth with combination of antibiotics is **antibiotic additive effect** where their concentration is equal to 50% of the MIC each antibiotic acting alone. The fraction of MIC (**FIC**) of an antibiotic required to inhibit the growth of bacteria. In comnination, when more than 50% of MIC of each antibiotic is required to inhibit the growth of bacteria, it is called **ineffective antibiotic combination**; indicates unviable combination of antibiotics. Under these circumstances of antimicrobial combination, the FIC is less than one, equivalent to one and more than one, respectively.

e) **Pharmacokinetic properties**: Penicillin G (destroyed by gastric acid), aminoglycosides (not absorbed orally) and chlorampenicol in ruminants (degraded by ruminal flora) cannot be given orally and are given parenterally. Aminoglycosides cannot pass through the blood brain barrier and are ineffective in bacterial meningitis; whereas, sulfadiazine, chloramphenicol, cefotaxime and rifampin can pass through B-B-B and attain high concentration in CSF and are the preferred drugs in meningitis. Penicillin cannot readily pass across the pleural or peritoneal membrane; whereas chlortetracycline does the same readily. Ampicillin and erythromycin attain high billiary concentrations and can be given in biliary tract infection.

f) **Dose of the AMA**: At the start the animal needs to be administered an initial **leading, loading dose** or **priming dose** to produce effective MAC, followed by repeating the dose intermittently at specified intervals and for required duration called **pulse dosing**. The pulse doses may be lesser than or equal to the initial dose, depending upon the AMA. The priming dose establishes the therapeutic antimicrobial concentration and the pulse doses continue to maintain that level; hence can also be called maintenance doses (sulfonamides). However, several antimicrobial or other drugs are administered at fixed predetermined intervals at the same dose level (similar initial and maintenance doses). Some antibiotics (aminoglycosides, fluoroquinolones and imepenem) exhibit antibacterial effect called post-antibiotic effect (**PAE**), which is a measure of the persistence of antibacterial action after the withdrawal of the antibiotic.

g) **Route of administration**: The effective plasma concentrations of AMA and their subsequent maintenance depend upon the route of administration of the drugs. The IV route is preferred in life threatening serious infections. Oral antimicrobial therapy is generally preferred in monogastric animals and young ruminants, but oral use of AMAs in ruminants is not advisable (because of erratic absorbtion in large rumen and destruction by ruminal microflora) except for enteric infections.

h) **Toxicity**: If a number of AMAs having similar efficacy can be used for the treatment of an infection, the least toxic AMA is preferred. Penicillins, cephalosporins and erythromycin are preffered over aminoglycosides, tetracyclines, chloramphenicol and vancomycin. An AMA should have **wide chemotherapeutic index** (ratio of median lethal dose to the median effective dose of a chemotherapeutic agent; wider the ratio safer the AMA; it is similar to therapeutic index of other drugs).

i) **The risk of development of drug resistance** among the microbes and **residues** in the milk, milk products, meat and eggs must be considered.

j) **Cost of AMA**: A less costly AMA is generally preferred to expensive one, without compromising the efficacy.

5. **Complications of Antimicrobial Therapy**

a. **Toxicity**: Many drugs like tetracyclines, erythromycin and chloramphenicol are irritants and may cause pain and abscess formation on IM injection or thromphlebitis of injected vein on IV injection. Different AMAs show their dose related characteristic organ toxicities e.g. aminoglycosides (ototoxic and nephrotoxic), tetracyclines (hepatotoxic and nephrotoxic), chloramphenicol (bone marrow depression and aplastic anaemia). But penicillins, certain cephalosporins and erythromycin are least toxic and they have high margin of safety.

b. **Allergic and idiosyncratic reactions**: All AMAs are foreign to the body and are capable of producing hypersensitivity reactions and this may be in the form of mild skin rashes or a severe anaphylaxis. Sulfonamides, penicillins, aminoglycosides and cephalosporins are most common offenders. Individuals genetically deficient in glucose-6-phosphate dehydrogenase enzyme when treated with primaquine, fluoroquinolones or sulfonamides may suffer from haemolysis. These reactions are independent of the dose of the drug and cannot be predicted.

c. **Superinfection**: It is the development of a new infection in the patient due to the use of AMA for chemotherapy. It is more common when broad-spectrum antibiotics such as tetracyclines, chloramphenicol etc or combinations of AMAs are used. Superinfection is more seen in intestine (causing fungal or bacterial enteritis), respiratory tract and urogenital tract (superinfection with *Proteus* and *Pseudomonas*). It can be avoided by using narrow spectrum antibiotic, whenever possible and by preventing indiscriminate use of antibiotics.

d. **Microbial drug resistance**: It is the insensitiveness of a microorganism to an AMA. (Staphylococcal resistance to penicillin G and *Enterococci* to streptomycin)

e. **Vitamin deficiencies**: Vitamins B and K are synthesized in the GI tract of man and animals. Use of AMA interferes with normal intestinal flora (particularly in herbivores) and therefore vitamin synthesis. This may result in vitamin deficiency in man and animals.

## 6. Microbial Resistance

When bacteria are no longer susceptible to the action of an antibiotic, the bacteria are said to have developed resistance to that antibiotic. Bacterial resistance to antimicrobials is of two types mainly: Natural and Acquired.

**Natural Resistance**: Some bacteria are inherently insensitive to a particular antibiotic. The *E. coli* bacteria are naturally resistant to benzylpenicillin (unable to penetrate the cell wall). Gram positive bacteria are usually susceptible to some antibiotics which are ineffective against Gram negative bacteria and *vice versa*.

**Acquired Resistance**: When previously sensitive bacteria become resistant to an antibiotic the process is called acquired resistance. This is due to replacement of sensitive bacterial population by resistant population. The acquired resistance is through genetical or biochemical mechanisms. Indescriminate use of antibiotics (improper selection of an antibiotic, under dosage or treatment for longer/shorter period than required) promotes acquired resistance.

**Genetic change** involves one or more of the following mechanisms:

a) **Mutation**: Some mutants that are relatively resistant to an antibiotic exist in a large susceptible bacterial population. This is due to sudden change in the chromosomes of such bacteria. The change is passed on to the succeeding generations, resulting in growth and multiplication of resistant mutants.

b) **Transmissible resistance**: The resistance is due to transfer of resistant genetic material from bacterium to the other through transduction, transformation or conjugation.

**Transduction** involves a bacteriophage (a virus that infects bacteria) which carries the DNA from the bacteria resistant to an antibiotic to new bacteria, which also subsequently become resistant to that antibiotic (transfer of penicillinase code among the *Staph. aureus* bacteria). The process occurs among both Gram positive and Gram negative bacteria

**Transformation** results from transfer of free DNA from one bacterial cell to the other. The recipient bacteria become resistant if the DNA codes for resistance.

**Conjugation** is the transfer of genes from one bacterium to another by a direct contact through a surface structure (sex pilus or bridge). The DNA coding for antibiotic resistance is transferred from the donor cell into the recipient cell (conjugal transfer). The recipients then turn into donors and the resistant population is built up rapidly. The conjugal transfer of resistant genes is reported in Gram negative bacteria; not only occurs between the bacteria of within the same species (*E. coli*), but also occurs predominantly between species of different species of Gram negative bacteria (between *E. coli* and *Salmonella* spp). Conjugation is the most common mode of developing resistance among bacteria.

**Biochemical mechanisms** that are responsible for development of resistance among once susceptible bacteria involve:

a) Antibiotic inactivation by enzymatic breakdown: Beta-lactamases on penicillins or cephalosporins. Chloramphenicol inactivation by chloramphenicol acetyltransferase and inactivation of aminoglycosides through enzyme-mediated phosphorylation, adenylation and acetylation

b) Decrease in the affinity of the bacterial binding site: Altered binding site on 50S ribosomal subunit against erythromycin, point mutation in DNA gyrase against fluoroquinolones and altered DNA-dependent RNA polymerase against rifampicin.

c) Reduced antibiotic accumulation through development of active-efflux mechanism by the bacteria: Tetracyclines, eryhthromycin and fluoroquinolones

d) Development of altered metabolic pathway to overcome the metabolic block by the AMA: Use of preformed folic acid against sulfonamides.

e) Promotion of formation of dihydropteroate synthetase with low affinity to sulfonamides, but not to PABA.

f) Reduced uptake by the bacteria: Ciprofloxacin and norfloxacin.

Another type of resistance, bacteria exhibit is **cross-resistance**, where the bacteria developing resistance to an antibacterial also become resistant to other antibacterials of similar type. This is due to identical mechanism of antibacterial action (Bacterial resistance to sulfonamides, tetracyclines, penicillins etc).

**How to curb drug resistance?** For clinical efficacy of an antibacterial it is essential to prevent drug resistance. To combat the problem of resistance, the following measures should be considered:

a) Every effort should be made to use antibiotics only when the clinical indications are clear. Do not use AMA if the disease is not infectious, untreatable or self limiting.
b) Information regarding endemic infections and sensitivity pattern should be considered before selection of an AMA.
c) Avoid overuse of newer AMA when an already available drug is equally effective.
d) If an AMA is needed, a narrow spectrum AMA should always be preferred whenever possible.
e) Prefer rapidly acting and bactericidal drugs particularly where host defense is impaired.
f) In combination of AMAs agianst resistant organisms, the individual agents should be used in full doses.
g) Broad-spectrum antibiotic should be used only when a narrow spectrum drug is not effective against the organism or unsuitable for the animal.
h) Indiscriminate use of AMA should be stopped.
i) AMA should not be used at sub-therapeutic dose or unnecessarily for a extended period.

## 7. Combination of AMAs (Antibacterial Agent)

In general AMAs should not be combined indiscriminately or without justification. But sometimes they are used in combination with specific objectives as below:

**i. To achieve additive or synergistic effects:** The rules regarding combinations are:
Bacteriostatic + Bacteriostatic = Additive/sometimes synergistic
Bactericidal + Bactericidal = Additive
Bactericidal + Bacteriostatic = Generally antagonistic.
Synergistic combinations are used in full doses of individual drugs for achieving the goal.

**ii. To broaden the spectrum of antibacterial activity:** It is necessary in the treatment of mixed infections and in severe undiagnosed bacterial infections. Combination should not be the substitute of accurate diagnosis.

**iii. To curb the development of drug resistance:** This is very important for the treatment of diseases where the organism is notorious for developing drug resistance and for chronic infections requiring prolonged antimicrobial therapy.

**iv. To decrease the intensity of toxic effects:** Drugs having low therapeutic index when used in their full doses precipitate toxicity. If such a drug is combined with another synergistic drug in reduced doses, it's toxicity can be reduced: When amphotericin B + Flucytosine combination is used for cryptococcal meningitis, a shorter course of treatment is needed than when amphotericin B is used alone.

**Disadvantages of Combination of AMAs:**

a) Increased chance of development of variety toxicity.
b) Improper combination results in increase in intensity of toxicity of a drug by another.
c) Promotion of development of resistance or increase in nephrotoxicity (Gentamicin + cephaloridine).
d) The chances of superinfections are increased.
e) Generate a causal rather than rational view in diagnosis of infectious diseases or selection of AMA.
f) Increase the cost of therapy.

### g. Chemoprophylaxis

It is the use of an AMA to prevent the setting in of an infection in the body or to combat a contacted infection before its final clinical manifestation. It reduces the number of the viable microbe below the critical level; thus preventing infection. The chemoprophylaxis may be done against specific organisms (generally highly satisfactoty e.g. Tuberculosis in man with isoniazid), for prevention of infection in some high risk situations e.g. urinary tract catheterization may be satisfactory but it is highly unsatisfactory and comdemnable even hazardous if it is done for prevention of infection in general.

## 10. Misuses of AMAs

a) **Treatment of untreatable diseases**: Use of antibitiotics in viral diseases.

b) **Improper dosage**: Antibiotics should be administered at adequate therapeutic doses. Their suboptimal dosage will not suppress the bacteria, and at the same time may precipitate development of resistant population. Administration of higher doses can cause toxicity to the host.

c) **Superinfections**: Use of oral antimicrobial therapy, especially the broad-spectrum antibiotics, suppresses the normal ruminal or intestinal microflora leading to development of enteric infections by the invading pathogenic microbes.

d) **Inhibition of starter bacteria**: Use of antibiotics in dairy animals results in excretion of significant levels of the antibiotics through milk, which may suppress the starter bacteria.

e) **Antibiotics as growth promoters**: Use of antibiotic-growth promoters in feed-lot animals before slaughter without observing withdrawal specifications may pose public health hazard.

f) **Applications of antibiotics in surgical wounds without proper drainage**: Use of antibiotics to prevent bacterial infections, without removal of necrotic tissue debris or providing proper drainage for the purulent exudate, results in markedly lowered antibacterial potency of the antibiotics.

## EXERCISE

1. Classify the antimicrobial agents based on mode of antimicrobial action giving suitable examples.
2. Describe how you select antimicrobial agents based on the infectious organism.
3. Describe how you select antimicrobial agents based on the infected animal.
4. Describe drug-related considerations in selection of an AMA while treating infectious diseases in animals.
5. Describe microbial resistance to antimicrobial drugs.
6. What is antimicrobial combination therapy? Discuss its advantages and disadvantages.

7. **Write a short note on the following**:
   a) Historical background of chemotherapy
   b) Selectivity of antimicrobials
   c) Principles of chemotherapy
   d) Complications of antimicrobial therapy
   e) Misuses of antimicrobials
   f) Genetic mechanisms of microbial resistance to antimicrobials
   g) Biochemical mechanisms of microbial resistance to antimicrobials
   h) Transmissible antimicrobial resistance of microbes
   i) Considerations to check microbial resistance to antimicrobials

8. **What do you mean by the following? Answer in one or two sentences for each**:
   a) Chemotherapy
   b) Antibiotic
   c) Selectivity of antimicrobials
   d) Cross resistance of microbes
   e) Chemotherapeutic index
   f) Bacteriophage
   g) Microbial drug fastness
   h) Pulse dosing
   i) Superinfection
   j) Chemoprophylaxis
   k) MIC
   l) MBC
   m) MAC
   n) FIC
   o) Chemotherapeutic index
   p) MFC
   q) PAE
   r) Conjugal transfer

9. **Differentiate between the following:**
   a) Bacterial cell wall and cell membrane
   b) Gram positive and Gram negative bacteria
   c) MIC and MAC
   d) MAC and MBC
   e) Antibiosis and symbiosis
   f) Acquired resistance and natural resistance
   g) Leading/Loading/Priming dose and maintenance dose
   h) Pharmacodynamic agent and chemotherapeutic agent
   i) Bacteriostatic and bactericidal
   j) Infection and superinfection
   k) Mutation and transduction
   l) Transduction and transformation
   m) Mutation and conjugation
   n) Bacteriophage and bacteria
   o) Prime dosing and pulse dosing

10. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
   a) Antibiotic sources: Fungi/Bacteria/Actinomycetes
   b) Paul Ehrlich: Father of chemotherapy/Chemotherapeutic index/Arsephenamine/Methyle blue
   c) Pasteur and Joubert: Concept of antibiosis between microbes
   d) Gerhard Domagk: Sulfonamides/Prontosil
   e) Alexander Fleming: Penicillin
   f) Waksman: Streptomycin/Antibiotic
   g) Inhibition of bacterial cell wall formation: Penicillins/Cephalosporins/Bacitracin/Cycloserine/Vancomycin
   h) Alteration of microbial cell permeability: Nystatin/Amphotericin B
   i) Inhibition of ergosterol formation: Itraconazole/Ketoconazole
   j) Cationic detergent antibiotic: Colistin/Polymixin B
   k) Inhibition of bacterial folate synthesis: Sulfonamides/Sulfones/Trimethoprim/Pyrimethamine/Proguanil
   l) Frameshift mutation: Proflavine/Acriflavine
   m) Inhibition of RNA polymerase: Rifamycin/Rifampin
   n) Inhibition of DNA gyrase: Ciprofloxacin/Norfloxacin/Fluoroquinolones/Quinolones
   o) Interfere with tRNA action on 30 S ribosomal subunit: Tetracyclines
   p) Aminoglycosides: Formation of abnormal codon/Misreading codon/Binding to 30 S ribosomal subuint
   q) Chlramphenicil: Binding to 50 S ribosomal subunit/Inhibition of transpeptidation
   r) Inhibition of peptide translocation: Erythromycin/Lincomysin
   s) Bind to 30 S subunit of bacterial ribosome: Tetracyclines/Aminoglycosides
   t) Bind to 50 S subunit of bacterial ribosome: Chloramphenicol/Erythromycin/Lincomycin
   u) Fungal origin: Penicillin/Cephalosporin/Griseofulvin
   v) Bacterial origin: Bacitracin/Polymyxin B/Colistin/Tyrothricin
   w) Actinomycetes origin: Streptomycin/Tetracyclines/Chloramphenicol/Macrolides
   x) Aminoglycosides: Ototoxicity-Nephrotoxicity/Curariform effect
   y) Tetracyclines: Hepatotoxicity-Nephrotoxicity
   z) Chloramphencol: Bone marrow depression/Aplastic anaemia/Grey baby syndrome
   aa) Transduction: Bacteriophage/Transmissible resistance
   bb) Mutation: Resistance in progeny or succeeding generations
   cc) Transformation: Transfer of DNA coding for resistance between bacteria
   dd) Conjugation: Contact transfer of resistance genes
   ee) Beta-lactamases: Penicillins/Cephalosporins
   ff) Activation of efflux mechanisms: Tetracyclines/Erythromycin/Fluoroquinolones
   gg) Altered metabolic pathway: Sulfonamides
   hh) Altered enzyme synthesis: Sulfonamides
   ii) Reduced bacterial uptake: Ciprofloxacin/Norfloxacin/Fluoroquinolones
   jj) Cross resistance: Sulfonamides/Tetracyclines/Fluoroquinolnes/Penicillins
   kk) Additive/Synergistic: Bacteriostatic+Bacteriostatic
   mm) Additive/Synergistic: Bactericidal+Bactericidal
   nn) Antagonistic: Bactericidal+Bacteriostatic
   oo) PABA antagonism: Sulfonamdes
   pp) Antibiotics with PAE: Aminoglycosides/Fluoroquinolones/Imipenem

11. **Substantiate each of the following by giving the most appropriate reason:**
   a) Penicillins/Cephalosporins do not affect mammalian cells
   b) Selective toxicity is the essential criterion in chemotherapy
   c) Antiviral/Anticancer drugs have low selectivity
   d) Paul Ehrlich is regarded as father of chemotherapy.
   e) Modern era of chemotherapy commenced with the discovery of Domagk.
   f) Golden age of chemotherapy began in the year 1941.

g) Penicillins/Cephalosporins/Streptomycin/Kanamycin/Colistin/Bacitracin/Polymixin B are bactericidal.
h) Sulfonamides/Tetracyclines/Chloramphenicol/Erthromycin/Lincomycin are/is bacteriostatic
i) Tetracyclines/Aminoglycosides/Chloramphenicil/Erythromycin/Lincomycin inhibit protein synthesis.
j) Sulfadrugs/Trimethoprim/Pyrimethamine/Proguanil/Rifampin/Fluoroquinolones inhibit folate synthesis.
k) Therapy of AMAs must be extended 2-3 days beyond the disappearance of clinical signs.
l) Antimicrobial therapy must be instituted as early as possible in the course of an infection.
m) Chloramphenicol toxicity in neonates is characterized by 'grey baby syndrome'.
n) Tetracyclines are contraindicated in newborns.
o) Sulfonamides will be ineffective in animals with immune deficiency.
p) Oral use of broad spectrum antimicrobials in animals results in superinfection.
q) Combination therapy of tetracyclines and chloramphenicol is synergistic.
r) Penicillin and streptomycin combination is synergistic.
s) In pneumococcal infection penicillin and tetracycline or chloramphenicol combination is not used.
t) Aminoglycosides are not used to treat meningitis
u) Sulfadiazine, chloramphenicol, cefotaxime and rifampin are the drugs of choice in treating meningitis.
v) In biliary tract infections ampicillin or erythromycin can be used.
w) Oral AMA therapy is not advisable in ruminants, except in enteric infections
x) Oral broad spectrum antimicrobial therapy causes vitamin K/B-complex vitamin deficiency in animals.
y) Cross resistance among bacteria appears through conjugation process.
z) Antimicrobial therapy should not be at sub-therapeutic doses or unduly extended.
aa) Antimicrobial combination therapy tends to curb microbial resistance.
bb) Antimicrobial combination therapy tends to reduce the severity of toxicity of individual drugs.
cc) Antimicrobial combination therapy broadens antimicrobial spectrum.
dd) Antimicrobial combination therapy may result in multitoxicity.
ee) Antimicrobial combination therapy may enhance the risk of superinfections.
ff) Antimicrobial drugs should not be used at sub-optimal doses.
gg) Use of antimicrobial growth promotants/feed supplements is of public health concern.
hh) Before antibacterial treatment, the wounds must be cleaned of pus and tissue debris.
ii) Bacteriostatic drugs are less effective in very young or debilitated animals.
jj) Bacteria becoming refractory to one sulfonamide also become insensitive to other sulfonamides.
kk) Sulfonamide discovery is of historical significance.
ll) MAC may be one-tenth of MIC/MAC is lesser than MIC.
mm) MIC is generally more than MAC.
nn) FIC is more than one in improper antibiotic combinations
nn) FIC is less than one or equivalent to one in successful antibiotic combinations.
oo) Higher the chemotherapeutic index, safer would be the antibiotic.
pp) Bactericidal antibiotic is recommended in immunologically compromised animals.
qq) Bacteriostatics will not control infection in immunologically compromised animals.

Q. Describe spectrum, mechanism of action & toxicity of Sulfonamides



## Chapter – 33: ANTIBACTERIAL DRUGS

### 1. Sulfonamides

Sulfonamides are the first AMAs effective against pyogenic bacterial infections. These are most widely used AMAs in veterinary medicine, mainly because of their relative efficacy in some common bacterial diseases in animals and of low cost.

**Chemistry**: All sulfonamides are derivatives of sulfanilamide (para-aminobenzene sulfonamide), the antibacterial component of an azo dye (prontosil). In the chemical structure of sulfonamide there is a sulfanilamide nitrogen designated as N1 and an amino nitrogen called N4. Most antibacterial sulfonamides have been synthesized by chemical substitution at N1 position. The individual members differ in the nature of N1 substitution, which governs the solubility, potency and pharmacokinetic property of the compounds. A free amino group in N4 position is essential for antibacterial activity and generally N4 substituted sulfonamides have reduced antibacterial activity. However, certain N4 substituted sulfonamides provide antibacterial action within the lumen of GI tract. They are white crystalline powders, insoluble in water.

**Classification**: Based on clinical uses:

**1. Sulfonamides used for systemic infections**:

a) **Short acting**: Highly absorbed and rapidly excreted (duration of action 4-8 hr): Sulfathiazole, sulfamethazine (sulfadimidine), sulfamerazine, sulfadiazine and sulfapyridine.

b) **Long acting**: Highly absorbed, but slowly eliminated (duration of action 1-3 days) because of high protein binding or lipid solubility (reabsorbed in renal tubules): Sulfamethoxypyridazine, sulfaethoxypyridazine, sulfadimethoxine and sulfachloropyridazine.

**2. Sulfonamides used to treat urinary tract infections**: Sulfisoxazole (sulfafurazole) and sulphisomidine: These are highly water soluble, rapidly excreted via urine, mostly unchanged, undergo least acetylation or acetylated crystals are highly soluble even in acid urine (so less propensity to cause crystalluria) and attain high concentration in urinary tract.

**3. Sulfonamides used to treat gut infections (Gut-active sulfonamides)**: These are poorly soluble and are not absorbed from GIT. Phthalylsulpfthiazole and succinylsulfathiazole are inactive as such and hydrolyse in the GIT by intestinal microflora to phthalic and succinic acid and active sulfathiazole. Sulfaguanidine or salicylazosulfapyridine (sulfasalazine) is also hydrolysed in large intestine to sulfapyridine and aminosalicylic acid (antiinflammatory agent) and is used in ulcerative colitis in dogs.

**4. Sulfonamides used topically:**

a) **To treat eye infection**: Sulfacetamide sodium: As 30% solution or 10% ointment (highly soluble and yield nonirritating neutral solution).

b) **To treat burn and wound infections**: Mafenide (sulfamylon) and silver sulfadiazine.

**Dosage of Sulfonamides in Animals**:

| Sulfonamide | | Adiministration (All species) mg/kg | |
|---|---|---|---|
| Type | Drug | Initial Dose | Maintenance |
| Systemic | Sulfadimidine (Sulfamethazine) | 220 (oral)<br>110 (SC/IV) | 110 (oral at 12-24 hr intervals)<br>100 (oral,SC or IV as 331/3% sterile solution once in a day) |
| | Suphadimethoxine | 60 (oral)<br>60 (SC/IV) | 30 (oral at 24 hr interval)<br>30 (SC/IV, 40% sterile solution at 24 hrs) |
| | Sulfathiazole | 66 (oral) | 66 (oral at 4-8 hr interval) |
| | Sulfamethoxypyridazine | 60 (oral) | 60 (oral once in a day) |
| | Sulfadimethoxine | 55 (oral) | 28 or as 40% solution @ 28 SC, IM or IV (oral once a day) |
| | Sulfapyridine | 140 (oral) | 70 (oral at 12 hr interval) |

| | | | |
|---|---|---|---|
| Enteric | Sufaguanidine | 200-300 (oral) | 150 (oral daily in two divided doses) |
| | Phthalylsulfathiazole | 150-200 (oral) | 150-200 (oral daily in two divided doses) |
| | Succinylsulfathiazole | 150-200 (oral) | 150-200 (oral daily in two divided doses) |
| | Phthalylsulfacetamide | 150-200 (oral) | 150-200 (oral daily in two divided doses) |
| Topical (Eye) | Sulfacetamide | | 30% solution or 10% ointment |

Sulfaquinoxaline is used in poultry in intestinal coccidiosis: @ 0.125% in feed as prophylactic or @ 0.05% in feed as curative.

**Withdrawal Periods**: For meat purpose: Pigs: 14 days; Cattle: 10 days; milk to be discarded for four days.

**Mechanism of Action of Sulfonamides**: Many bacteria synthesize their own folic acid for which p-aminobenzoic acid (PABA) is an essential constituent. Sulfonamides are structural analogs or competitive antagonists of PABA. They are competitive inhibitors of dihydropteroate synthetase, a bacterial enzyme responsible for the union of PABA with pteridine residue in bacterial formation of dihydropteroic acid which further conjugates with glutamic acid to produce dihydrofolic acid. The antagonism thus leads to inhibition of synthesis of folic acid and subsequent metabolites resulting in bacteriostatic effect.

Pteridine residue + PABA

**Blocked by Sulfonamides** ↓ Dihydropteroate synthetase enzyme

Dihydropteroic acid

↓ + Glutamic acid

Dihydrofolic acid

**(Blocked by Trimethoprim)** ↓ Bacterial dihydrofolate reductase( DHRFase) (NADP reduced to NADPH)

Tetrahydrofolic acid

↓

Purines and pyrimidine synthesis

↓

Nucleic acid synthesis

↓

**Cell division leading to bacterial multiplication and growth**

The organisms, which synthesize their own folic acid and cannot utilize preformed folic acid are sensitive to sulfonamides. Sulfonamides do not affect mammalian cells since they require preformed folic acid supplied in diet and need not synthesize it.

**Principles of Sulfonamide Therapy:**

a) Sulfonamides should be administered as early as possible in the course of an infection (active growth/multiplication of bacteria and active cellular and humoral defense mechanisms and prompt phagocytosis).
c) In severe infection larger dose should be given by parenteral route (IV or IM).
d) The initial large dose should be followed by regular smaller maintenance doses.
e) Plenty of water and urinary alkaliser (sodium bicarbonate) is to be given with sulfa drugs to prevent crystalluria.
f) If there is any sign of anuria and haematuria sulfa therapy should be stopped and plenty of water and urinary alkaliser is to be given.
g) Sulfonamides should not be given for more than one week because it may cause interference with normal flora and vitamin synthesis and cause development of drug resistance.

h) If response does not occur within first 2-3 days, suphonamide therapy should be stopped as no response could then be expected.
i) As sulfonamides are bacteriostatics, their dosing should be continued for about 48 hr after the disappearance of clinical symptoms, otherwise there might be a relapse of infection/disease.

**Administration and Pharmacokinetcs:**
Sulfonamides are administered orally, IV (in acute cases), IM, SC, IP, intrauterine or topically. The parent sulfonamides are administered by oral or topical route. The monosodium salts of most sulfa drugs are given IV, but not by other parenteral routes (less solubility and cause severe irritation). The disodium salts can be used for IV as well as IM or SC administration (highly water soluble). Sulfonamides following oral administration are rapidly and completely absorbed from the GI tract in dogs and cats; whereas ruminants take much longer time and oral absorption in pigs and horses is intermediate. Absorption is rapid from parenteral sites. Sometimes to achieve therapeutic blood levels rapidly, the drugs are administered IV or by deep IM injection, and subsequently orally to maintain the blood levels. The therapeutically effective blood levels are 8-15 mg/ 100 ml in man and 5 mg/ 100 ml in animals.

The extent of plasma protein binding of different sulfonamides varies considerably (10-90%). Highly protein bound sulfonamides are long acting. These drugs are widely distributed throughout the body including the serous cavities. The free form of sulfadiazine has good penetrability into brain and CSF, therefore it is the preferred sulfonamide in the treatment of meningitis.They cross placenta freely and also diffuse into milk.
The primary pathway of metabolism of sulfonamides is acetylation at N4 by hepatic microsomal enzyme. The extent of metabolism differs for different sulfonamides and in different species. The acetylated derivatives have little antibacterial activity, but contribute to adverse effects. Most of the N4 acetylated sulfonamides, except the sulfapyrimidine derivatives (sulfadiazine, sulfamerazine and sulfadimidine) are less soluble in acid urine, precipitate in the tubles and cause crystalluria. The combination of these three sulfonamides in the form of 'triplesulfa' has added antibacterial effect with minimized risk of crystalluria.
Most of the sulfonamides are excreted mainly in urine through glomerular filtration. Both renal tubular secretion and reabsorption (lipid soluble) contribute to renal excretion of sulfonamides. Lipid soluble sulfonamides are reabsorbed in renal tubules and hence are long acting. The crystalluria can be prevented by alkalinizing the urine, increasing water intake and reducing the dose rates or by using triple sulfa.

**Antagonists of Sulfonamides:**
.a) Compounds containing PABA nucleus such as local anaesthetics (procaine, butacaine and benzocaine), procainamide and procaine penicillin.
b) Nicotinamide, folic acid and choline and their precursors.
c) Gelatin, albumin, peptone and serum protein (with which the sulfa drugs bind).
d) Antibacterial action is neutralized in the presence of pus or tissue breakdown products (contain thymidine and purines which are utilized by bacteria bypassing the need of folic acid).

**Synergists of Sulfonamides**: Diaminopyrimidine (DAP) derivatives like trimethoprim act synergistically with sulfa drugs, by inhibiting dihydrofolate reductase (sequential blockade) in PABA-Nucleic acid synthesis pathway (see below).
**Clinical Uses of Sulfonamides**: Sulfa drugs are used for the prevention and treatment of acute systemic and local (GI, urinary tract, topical) infections. The diseases cured by sulfonamides are actinobacillosis, actinomycosis, strangles (horses), coccidiosis, mastitis, metritis, colibacillosis, infectious polyarthritis, infectious keratitis, pneumonia, respiratory infections, urinary tract infections, pododermatitis, toxoplasmosis, meningitis and foot rot.

**Adverse Reactions of Sulfonamide Therapy:**
Impairment of renal function is a common adverse reaction:

**Renal Toxicity**: It is characterized by crystalluria, haematuria and obsruction of renal tubules. The drugs crystalize in acid urine. Crystalluria is more common with rapidly excreted sulfonamides than those excreted slowly. The renal damage is also more common with their acetylated derivatives (due to less solubility in acid urine) as compared to their glucuronide or sulfate conjugates, which are highly soluble. The clinical signs of renal impairment include crystalluria, renal colic, repeated attempts to urinate and elevated BUN levels. Crystalluria is more common in carnivores (Dog/Cat), which excrete acid urine than in herbivora, which excrete alkaline or neutral urine. Adequate water intake and alkalinization of urine (sodium bicarbonate) reduce the risk of crystalluria.

**Toxicity of Sulfonamides**:

**Acute**: Rare, but occurs when administered at high doses, particularly by IV route in dog, cat, calves and swine. The acute toxicity signs include salivation, vomiting, diarrhoea, excitement, hyperpnoea/dyspnoea, muscle weakness, ataxia and rigidity or spasticity of limbs.

**Chronic**: Haematological alterations are common (agranulocytosis, haemolytic anaemia, reduction in cell counts and haemoglobin level). Vesicle haemorrhages, hepatic degeneration, cyanosis, jaundice, peripheral neuritis (sciatic and brachial nerves) and myelin degeneration (spinal cord and peripheral nerves) occur in dog and cat. Poultry show drop in egg production, abnormal eggs, hepatic and renal insufficiency, anaemia, agranulocytosis and hypoprothrombinaemia.

## 2. Potentiated Sulfonamides

These constitute the sulfonamides in combination with trimethoprim, which potentiates the antibacterial action of the former.

**Trimethoprim**: It is a diaminopyrimidine derivative. The antibacterial spectrum of trimethoprim is similar to sulfonamides, in addition also effective against some sulfonamide resistant organisms like *S. typhi*, *E.coli*, *Klebsiella*, *Haemophyllus* etc. It is a bacteriostatic drug and acts by selectively inhibiting bacterial dihydrofolate reductase enzyme. Its combination with sulfonamides results in potentiation of antibacterial action by sequential blockade at two steps in bacterial folate metabolism in nucleic acid synthesis. Trimethoprim, resembling pteridine moiety of folate, selectively blocks bacterial dihydrofolate reductase (DHFRase) and produces bacteriostatic effect. Individually both sulfonamide and trimethoprim are primarily bacteriostatic, but their combination is bactericidal. Trimethoprim has 50,000 times more inhibitory effect against bacterial DHFRase than against the mammalian enzyme. Therefore, it does not interfere with folate metabolism in mammals at antibacterial concentrations.

The common combinations are trimethoprim + sulfamethoxazole (cotrimoxazole), trimethoprim + sulfadoxine or trimethoprim + sulfadiazine in a ratio of 1:5. The combination can be given either orally (rapid absorption) or parenterally and also reduces the toxicity of sulfonamides. The antibacterial spectrum of the potentiated sulfonamides covers both Gram positive and Gram negative organisms (*Actinomyces, Bacillus anthracis, Brucella, Cornyebacterium, E. Coli, Haemophilus, Klebsiella, Pasteurella, Proteus, Salmonella, Staphylococci* and *Sterptococci*).

**Adminstration and Dosage of Potentiated Sulfonamides**:

A. **Sulfadiazine + Trimethorim**:
   g) Parenteral: A solution containing 400 mg sulfadiazine and 80 mg trimethoprim @ 1-5 ml/30 kg once in a day.
   h) Oral: In the form of bolus containing 1 gm of sulfadiazine and 0.2 gm of trimethoprim @ 30 mg/kg once in a day. (In the form of suspension containing 400 mg sulfadiazine and 80 mg of trimethoprim in one ml @ 15 mg/kg for five days. As tablets containing 400 mg sulfadiazine and 80 mg trimethoprim @ 15 mg/kg twice daily in dog and @ 120 mg once daily in cats).
   i) Intrauterine Bolus: Cow and Mare: 2.4-4.8 gm; Sow and Ewe: 1.2-2.4 gm.

B. **Sulphadoxine + Trimethoprim**: Parenteral: A solution containing 200 mg sulphadoxine and 40 mg trimethoprim @ 1 ml/10-15 kg IV once in a day.

## 3. Nitrofurans

These are a group of synthetic antibacterial compounds which contain a furan ring to which a nitro group is attached. The 5-nitro group is essential for their antibacterial action. They are broad spectrum antibacterials effective against both Gram positive and Gram negative bacteria (but mainly used against Gram negative bacteria like *E.coli, Salmonella, Klebsiella* and *Bacteroides* species) and also against *Coccidia, Giardia* and amoebae.

The nitrofurans are bactericidal or bacteriostatic in action. Their exact mode of action is not known.They act by inhibiting the enzymes necessary for the carbohydrate metabolism of bacteria. They are also thought to be converted to some metabolites (in bacterial cells) which interfere with the function of DNA. The antibacterial activity of nitrofurans is reduced in the presence of blood, pus and milk. Toxic manifestations of these drugs include vomtion, diarrhea, peripheral neuritis, allergy and ocular disturbances. These drugs are not used systemically because of toxicity but used for control of local or topical infections.

**Nitrofurazone:** Main indications include treatment of bovine mastitis, bovine metritis and skin, burn and wound infections. It is also used as feed additive @ 0.05% to control intestinal bacterial and coccidial infections.

**Nitrofurantoin:** It is mainly used as an urinary antiseptic for the prevention and treatment of urinary tract infections particularly in small animals. It is concentrated in acid urine (not precipitated), hence beneficial in dog (@ 4-5 mg/kg, orally, thrice daily for 5-10 days). Also used in calves and horse @ 10 mg/kg/day, orally for 10 days.

**Furazolidone:** It has broad range antimicrobial spectrum; effective against both Gram positive and Gram negative bacteria and *Eimeria* and *Histomonas* spp. It is mainly used orally to treat enteric infections. Calves: @10-12 mg/kg, orally twice a day for about a week; Poultry @ 0.04% in feed for 10 days.

**Furaltadone:** It is easily absorbed grom GIT and has medium antibacterial spectrum. It is used to treat bovine mastitis (@ 500 mg/quarter intramammarily); strangles in horse (@ 13 mg/kg, IV for 5 days) and salmonellosis in chickens (@ 0.04% in drinking water).

**Other Nitrofurans:** Nifuroquine (used in bacterial and *Mycoplasma bovis* mastitis), Nifuraldezone (for control of bacterial enteritis in calves) and Nifurprazine (topically in bacterial infections).

## 4. Sulfones

**Dapsone** (4, 4-diaminodiphenyl sulfone, DDS) is the sulfone used as an antibacterial agent. It is chemically related to sulfonamides. It is effective against *Mycobacterium laprae*. Like sulfonamides it inhibits folate synthesis in sensitive bacteria through PABA antagonism. Sulfone is the drug of choice for treatment of leprosy in man. It is not commonly used in other bacterial diseases due to its potent toxicity (haemolysis, methaemoglobinaemia, anorexia, nasuea and vomiting). The other antileprosy drugs are rifampicin and ethionamide (antiTB drugs), clofazimine and oil of *Chaulmoogra hydnocarpus*.

### EXERCISE

1. Classify the sulfonamides based on their clinical application and describe the principles of their therapy.
2. Describe the mode of antibacterial action of sulfonamides and discuss their pharmacokinetics.
3. **Write a short note on the following:**
   a) Principles of sulfonamide therapy
   b) Antagonists and synergists of sulfonamides
   c) Adverse reactions and toxicity of sulfonamides
   d) Enteric sulfonamides
   e) Potentiated sulfonamides
   f) Sequential blockade
   g) Nitrofurans
   h) Sulfones
4. **What do you mean by the following? Answer in one or two sentences for each:**
   a) Triple sulfa
   b) Crystalluria
   c) Sequential blockade
   d) PABA

5. **Differentiate between the following**:
   a) Sulfacetamide and phthalylsulfacetamide
   b) Sulfonamide and potentiated sulfonamide
   c) PABA and PABS
   d) Sulfadiazine and trimethoprim
7. **Describe the mechanism of action of the following drugs**:
   a) Sulfonamides
   b) Trimethorprim
   c) Nitrofurans
   d) Sulfones
8. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
   a) Short acting sulfonamide: Sulfathiazole/Sulfamethazine/Sulfamerazine/Sulfadiazine/Sulfapyridine
   b) Long acting sulfonamide: Sulfamethoxypyridazine/Sulfaethoxpyridazine/Sulfadimethoxine/Sulfachloro-pyridazine
   c) Sulfonamide for urinary tract infections: Sulfisoxazole/Sulfisomidine
   d) Gut active sulfonamides: Sulfaguanidine/Phthalylsulfathiazole/Succinylsulfathiazole/Phthalylsulfacetamide
   e) Topical/Eye sulfonamide: Sulfacetamide
   f) Sulfonamide for burn/wound infections: Mefenide/Sulfamylon
   g) Sulfonamide used in avian coccidiosis: Sulfaquinoxaline
   h) Monosodium salts of sulfonamides: IV route
   i) Disodium salts of sulfonamides: IV, IM, SC or oral routes
   j) Potentiated sulfonamide: Trimethoprim+sulfadiazine/Trimethoprim+sulfadoxine
   k) Dapsone: Sulfone/DDS/AntiTB/Antileprosy
   l) Sulfonamides: Crystalluria/Renal toxicity
   m) Therapeutic antibacterial concentration of sulfadrugs: 5 mg/100 ml.

9. **Substantiate each of the following by giving the most appropriate reason**:
   a) Bacteria which utilize preformed folic acid are insensitive to sulfonamides.
   b) Sulfonamides do not prevent mammalian cell division
   c) Sulfonamides exert bacteriostatic effect.
   d) Procaine/butocaine/Procaine penicillin antagonizes sulfonamide bacteriostasis.
   e) Antibacterial action of sulfonamides is neutralized by pus or tissue debris.
   f) B-complex vitamins antagonize sulfa-bacteriosis.
   g) Trimethoprim is synergistic with sulfa drugs.
   h) Sulfonamide-trimethoprim mode of action as antibacterials is through sequential blockade.
   i) Carnivora are more prone to the risk of sulfa-induced renal toxicity.
   j) Urinary alkalizers reduce the risk of sulfa-induced renal toxicity.
   k) Acetylated sulfonamides cause crystalluria, but their glucuronide conjugates are not.
   l) Lipid soluble sulfonamides are long acting.
   m) Sulfisoxazole/Sulfafurazole/Sulfisomidine is used to treat urinary tract infections.
   n) Sulfamethoxypyridazine/Sulfaethoxypyridazine/Sulfadimethoxine/Sulfachloropyridazine is a long acting sulfonamide.
   o) Sulfathiazole/Sulfamethazine/Sulfamerazine/Sulfadiazine/Sulfapyridine is a short acting sulfonamide.
   p) Phthalylsulfathiazole/Succinylsulfathiazole is an enteric or gut active sulfonamide.
   q) Salicylazosulfapyridine is used in ulcerative colitis in dogs.
   r) Sodium sulfacetamide is use as a topical sulfa-drug to treat eye infections.
   s) Sulfonamides act as PABA antagonists.
   t) Sulfonamides inhibit PABA utilization by bacteria.
   u) Sulfa-antibacterial therapy must be instituted as early possible in the course of an infection.
   v) Sulfonamide therapy must be continued for 48 hr after disappearance of clinical symptoms.
   w) Sulfadiazine is the choice of sulfa-drugs in treating meningitis.
   x) Triple sulfa is an ideal sulfa-drug combination.
   y) Lipid soluble sulfonamides are long acting.
   z) Diaminopyrimidine derivatives are synergistic with sulfonamides.
   aa) Trimethoprim inhibits bacterial DHFRase.
   bb) Trimethoprim does not interfere with folate metabolism in mammals.
   cc) Nitrofurans are broad spectrum antimicrobials.
   dd) Nitrofurantoin is used to treat urinary tract infections.
   ee) Furazolidine has broad range antimicrobial spectrum.

10. **Give the dose, route and administration for the following**:
    a) Sulfadimidine/Sulfaguanidine in cattle
    b) Phthalylsulfathiazole in calves
    c) Nitrofurantoin in a dog with urinary tract infection
    d) Potentiated sulfa in a buffalo with a systemic bacterial infection.

# Chapter- 34: ANTIBIOTICS

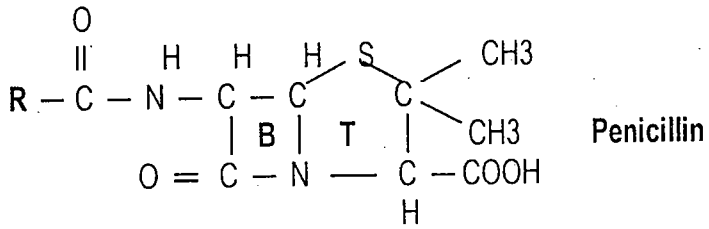
## 1. Beta-Lactam Antibiotics

These antibiotics have a beta-lactam ring as the essential antibacterial component in their chemical structure. The antibiotics under this group consist of penicillins, cephalosporins, cephamycins, monobactams and carbapenems.

### Penicillins

**Source:** Penicillin was originally discovered by Sir Alexander Fleming in the filtrate of culture medium of mold *Penicillium notatum* having bactericidal action on *Staphylococci* in 1929. *P. chrysogenum*, a mutant of *P. notatum* is presently used for commercial production of the antibiotic. Penicillin was the first antibiotic to be used clinically in 1941 signalling commencement of golden era in chemotherapy.The natural penicillin is benzylpenicillin (Penicillin G), which is 6-aminopenicillanic acid with a benzyl side chain.

**Chemistry:** The basic structure of penicillin comprises of a thiazolidine ring (T), connected to a beta-lactam ring (B), to which a side chain (R) is attached through an amide linkage. The side chain of natural penicillin can be split off by amidase to produce 6-aminopenicillanic acid (weak antibacterial activity). The natural penicillin is known as benzylpenicillin or Penicillin G and it is thermolabile and acid labile. Penicillin salts are formed by replacing H with Na and K from the carboxyl group attached to the thiazolidine ring. These salts are highly soluble and more stable than the parent acid. They are stable in dry state, but deteriorate rapidly at room temperature. Therefore, penicillin G solutions are always prepared freshly. The semisynthetic penicillins have been developed by adding different side chains to it, with unique antibacterial activity and variable pharmacokinetic properties. The bacteria, which elaborate the enzyme penicillinase, a beta-lactamase, are resistant to penicillins. The enzyme breaks the beta-lactam ring (BL) and inactivates peincillin through formation of penicilloic acid, which does not possess antibacterial activity.




Penicillin

BL

**Antibacterial spectrum**: Benzylpenicillin has narrow spectrum activity; effective against Gram positive organisms especially against cocci, but not against Gram negative organisms, except, a few. In general, viruses, fungi, rickettsiae, Chlamydiae, acid fast bacilli and majority of Gram negative bacteria are insensitive to penicillin G. It is bactericidal at 0.5 U/ml concentration. Its action is unaltered by blood, pus or tissue breakdown products. The extended spectrum penicillins are active against both Gram positive and Gram negative organisms.

**Classification of Penicillins**: Penicillins are classified into various groups based on their source: Natural penicillins and semisynthetic penicillins.

A. **Natural penicillins**:

a) Soluble sodium or potassium salts of benzylpenicillin (Penicillin G): Destroyed by gastric acid (orally inactive) and penicillinase. Given IV, IM or SC, onset of action within half an hour and duration of action only 3 hours.

b) Sparingly soluble organic salts of penicillin G or repository penicillins:

i) Procaine penicillin G: Admnistered IM (never IV), onset of action within 6-8 hours, destroyed by gastric acid and by penicillinase and duration ofction 12-24 hours. Incidence of hypersensitivity reaction is most common.

ii) Benzathine penicillin G: Administered IM (never IV), onset of action slow and duration of action one week.

**B. Semisynthetic penicillin:**

a) Acid-Resistant Penicillins:
   i) Phenoxymethylpenicillin (Penicillin V)
   ii) Phenoxyethylpenicillin (Phenethicillin)

b) Penicillinase resistant penicillins:
   i) Acid labile penicillins: Methicillin and nafcillin.
   ii) Acid resistant penicillins: Flucoxacillin, oxacillin, cloxacillin and dicloxacillin.

c) Extended spectrum penicillins: These are not penicillinase resistant.
   i) Amino penicillins: Effective against Gram positive and Gram negative bacteria: Ampicillin, bacampicillin, talampicillin, pivampicillin and amoxicillin.
   II) Carboxypenicillins: These are active against *Pseudomonas aeruginosa* and *Proteus* spp, but ineffective against *Klebsiella* and Gram positive cocci: Carbenicillin and ticarcillin.
   iii) Ureidopenicilins: Active against *Pseudomonas* and *Klebsiella*: Mezlocillin and piperacillin.
   iv) Amidinopenicillins: Mecillinam and pivmecillinam: Theses are highly active against Gram negative bacilli (*E.coli, Salmonella, Klebsiella* and *Enterobacter*, but not against *Pseudomonas* and Gram positive cocci.

Execept B (b) all the other penicillins are resistant to penicillinase.

**Mechanism of Action:** The Gram positive bacterial cell wall comprised of peptidoglycan having linear strands of two alternating amino sugars, N- acetyl glucosamie (NAG) and N- acetyl muramic acid (NAMA) which are cross linked by peptide chains (transpeptidation) and give rigid mechanical stability to the cell wall. Penicillin blocks the cell wall synthesis by inhibiting transpepdase enzyme and other proteins (penicillin binding proteins: **PBP**) that cross-link the peptide side chains of the sugar residues. The final bactericidal effect is due to inactivation of an inhibitor of the autolytic enzymes in the bacterial cell wall. Penicillin G is ineffective against Gram negative bacteria as it cannot penetrate their cell wall which contains an extra lipopolysaccharide layer. Ampicillin can penetrate Gram negative bacterial cell wall.
The hypersensitive reaction of penicillin is caused by the degradation products of penicillin which combine with host protein to act as hapten and become antigenic.

**Pharmacokinetics**: Penicillin G, its salts and methicillin are destroyed by gastric acid and are orally ineffective. Only the acid resistant penicillins like ampicillin, penicillin V, cloxacillin, oxacillin, amoxicillin can be given orally and their peak plasma concentration is reached within about two hours. Most of the penicillins including repository penicillins are administered parenterally (usually IM).
Penicillins are widely distributed in the body fluids and tissues. They can cross the blood brain barrier in subtherapeutic concentration in the presence of inflammation of meninges only. Inflammation also permits effective levels of certain penicillins in abscess and in pleural, peritoneal and synovial fluids. Their protein binding ranges from 20% (ampicillin) to 80% (cloxacillin).
Penicillins are chiefly excreted through kidney (90%) unchanged in urine. Out of which 20% is by glomerular filtration and 80% by proximal tubular secretion. The tubular secretion of penicillin is inhibited by probenecid prolonging the effective blood level of penicillins. Some broad spectrum semisynthetic penicillins are also excreted through the bile.

**Clinical Uses of Penicillins**: The penicillins are used in the treatment of local and systemic infections caused by the sensitive bacteria. Penicillin G is of value in the treatment of bovine mastitis (primarily in streptococcal mastitis), anthrax, Erysipelothrix infection in sheep, pigs and birds, Strangles in horses, clostridial infections (tetanus and black quarter), pyelonephritis and lumpy jaw in cattle, beta-haemolytic streptococcal infection in puppies, Meningococcal meningitis and in leptospirosis.

**Administration and Dosages of Penicillins:** The dosage of penicillin G is usually expressed as units. One standard unit of penicillin is defined as the amount of antibacterial activity present in 0.6 µgm of pure crystalline standard sodium penicillin G (1 mg = 1667 Oxford units). The dosage of semisynthetic penicillins is expressed in mg/kg. The sodium salt of benzylpenicillin is the most commonly used preparation for IM injection. When it is required for maintaning sustained antibiotic levels in the body it is used as relatively less soluble organic salts such as proaine benzylpenicillin or benzathine penicillin. Such injections need to be repeated once in a day or two. The peinicillin G preparations are ineffective when given by oral route due to inactivation by gastric acidity and intestinal flora.

| Penicillin | Dosage (All species) | Route | Interval |
|---|---|---|---|
| Benzathine penicillin G | 10,000-40,000 IU/kg | IM (Horse); SC (Cattle) | 48-72 hr |
| Penicillin V | 15,000 IU/kg | Oral | 8 hr |
| Sodium penicillin G | 10,000-20,000 IU/kg | IV or IM | 6 hr |
| Procaine penicillin G | 25,000 IU/kg<br>10,000-30,000 IU/kg | Oral<br>IM or SC | 6 hr<br>12-24 hr |
| Ampicillin | 5-10 mg/kg<br>10-25 mg/kg | IV, IM or SC<br>Oral | 8-12 hr<br>6-12 hr |
| Amoxicillin | 4-8 mg/kg<br>12 mg/kg | IM<br>Oral | 12-24 hr<br>12 hr (dog)<br>12-24 hr(Cat) |
| Carbenicillin | 10-20 mg/kg | IV or IM | 8-12 hr |
| Cloxacillin | 10 mg/kg | IM or Oral | 6 hr |

In the treatment of bovine mastitis (*Strep. agalactiae*) penicillin G is administered systemically or by intramammary infusion @ 300 000 units/quarter thrice in a day.

**Withdrawal Periods (WP) following Penicillin Therapy:**

| Penicillin | WP for meant (days) | Milk Discard Period (days) |
|---|---|---|
| Pracine Penicillin | 7-10 | 3 |
| Benzathine Penicillin | Cattle: 30 | |
| Amoxicillin (IM) | Cattle: 30 | 2 |
| Ampicillin (IM) | Cattle: 6; Calves: 15 | |

**Repository Penicillins:** Benzathine penicillin G and procaine penicillin G in oil. These are the penicillins which are slowly absorbed over a period of 5-7 days following a single IM injection. Probenecid delays renal excretion of penicillns and prolongs the blood levels of penicillins with short plasma half-life. It is added @ 1-2 mg/1000IU of penicillin G for oral dosing in dog at 6 hr intervals. The repository forms of penicillin should never be injected IV.

**Adverse Reactions and Toxicity of Penicillin:** Hypersensitive, allergic or anaphylactic reactions (mostly along with streptomycin) are reported in dog, cattle and horse following prior sensitization to the antibiotic. The clinical signs noted were salivation, shivering, vomition and urticaria in cat and dog, laboured breathing, salivation, cutaneous oedema (head and perinial region) and froth from nostrils and mouth in cattle and urticaria and pruritis in horse.

Penicillin toxicity is uncommon in animals. It is recorded in swine erysipeals when pregnant pigs are treated with benzathine penicillin (IM). Pigs show shivering, depression, anorexia, cyanosis, vomiting and pyrexia. IV injection of high dose of sodium benzyl penicillin (2,00,000 units or more/kg) was observed to cause severe acute toxicity characterized by neurological disturbances (ataxia and convulsions) in cat and dog.

**Beta-lactamases** are enzymes produced by penicillin-resistant bacteria, which break the antibiotic into inactive penicilloic acid. They are named as beta-lactamases as they act by splitting the beta-lactam ring present in beta-lactam antibiotics, penicillins and cephalosporins (BL in penicillin structure, see above). The enzymes are of two types: Penicillinase and Cephalosporinase.

**Beta-lactamase inhibitors:** These potentiate or reestablish the antibacterial potency of penicillinase sensitive penicillins against beta-lactamase producing organisms by inhibition of the enzyme (suicidial inhibition). These inhibitors are structurally similar to penicillin and act as substitutes for penicillinase (β-lactamase) causing inhibition of the enzyme.

1. **Clavulanic acid**: Obtained from *Streptomyces clavuligerus*, has no antibacterial activity of its own. It is generally combined with amoxicillin (Augmentin) or ticarcillin (Timentin).
2. **Sulbactam**: A semisynthetic beta-lactamase inhibitor, related chemically and in activity to clavulanic acid. It is combined with ampicillin and preferably for oral and parenteral administration.
3. **Tazobactam**: It is similar to sulbactam and combined with piperacillin.

**Potentiated Penicillins:** The penicillins in combination with beta-lactamase inhibitors are called as potentiated penicillins. The combinations are:
Clavulanic acid-amoxicillin (2:1), clavulanic acid-ticarcillin (15:1) and sulbactam-ampicillin.
Dose: Potassium clavulanate: amoxicyllin (1:4) @ 10-20 mg/kg (amoxicillin) and 2.5-5 mg/kg (clavulanate) orally at 12 hr.
Penicillins with sulbactam and tozobactum are administered IV; whereas, those with clavulanic acid are administered orally or IV.

**Cephalosporins**
These are semisynthetic antibiotics obtained by making different substitutions in 7-aminocephalosporanic acid of cephalosporin C produced by mold belonging to *Cephalosporium* (*C. acremonium*).

**Classification**: Based on route of administration:

a) First Generation: Oral: Cephalexin, cephradine, cefadroxil, cephalogylcin
Prarenteral: Cefapirin, cefazolin, cephalothin, cephalonium
Intramammary: Cefacetrile, cefapirin, cephalonium

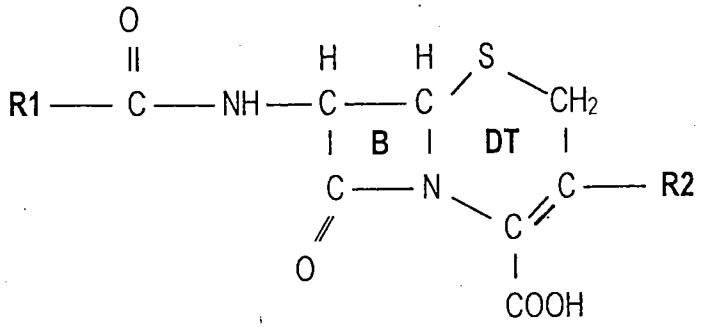
b) Second Generation: Oral: Cefachlor
Parenteral: Cefamandole, cefonicid, ceforonide, cefotoxifin, cefuroxine
Intramammary: Cefuroxime

c) Third generation: Oral: Cefixime
Parenteral: Cefmenoxine, ceftiofur, cefoperazone, cefotaxime, cefsulodin, ceftazidime, ceftizoxime, ceftriaxone, ceftibuten

d) Fourth generation: Parenteral: Cefepime and Cefpirome.

**Chemistry:** The cephalosporin molecule contains a 7-amino cephalosporanic acid consisting of a beta-lactam ring (B) like penicillins and dihydrothiazine (DT) unlike penicillins. Unlike the 6-aminopenicillanic acid of penicillins, the 7-aminocephalosporanic acid molecule in cephalosporins provides more sites (R1 and R2) for chemical manipulation in the production of many semisynthetic cephalosporins.

**7-Aminocephalosporanic acid**



**Antibacterial Spectrum:**

**I Generation** Cephalosporins have high activity against Gram positive, but are only with moderate to weaker activity against Gram negative organisms, relatively susceptible to cephalosporianse and are not effective against anaerobes.

**II Generation** Cephalosporins are more active against Gram negative and Gram positive organisms and relatively resistant to beta-lactamase.

**III Generation** Cephalosporins are more effective agianst Enterobacteriaceae (including beta-lactamase positive strains) and much less active against Gram positive. Some cephalosporins (cefoperazone, ceftazidime and cefuroxime) have good activity against *P. aeruginosa*, and are very much resistant to beta-lactamases of Gram negative bacteria. Most of them can penetrate blood-brain barrier and frequently indicated in bacterial meningitis.

**III Generation** Cephalosprins have activity comparable to III generation, but highly resistant to some beta-lactamases.

Cross-resistance is less among bacteria to penicillins and cephalosporins. The cephalosporins are ineffective against cephalosporinase (beta-lactamase) producing bacteria. The cephalosporinase splits the antibiotics into microbially inactive cephalosporanic acid. The enzyme also attacks penicillins.

**Mechanism of Action:** Cephalosporins interfere with bacterial cell formation by interfering with transpeptidation by inhibiting transpeptidases, similar to penicillins.

**Clinical uses:**

a) I Generation cephalosporins are used as alternative to penicillin G in Staphylococcal infection (cephalexin) and for surgical prophylaxis (cefazolin).
b) Ceftiofur is specifically used in bovine bronchopneumonia caused by *P. multocida* or *P. haemolytica* and in urinary tract infections in dogs.
c) Cephalosporins are useful in treating infections of soft tissues and bones, meningitis, osteomyelitis, prostatitis, arthritis and urinary tract infections.
d) Cephapirin benzathine (in dry cows) and cephapirin sodium are used in the treatment of mastitis.

**Administration and Dosage:**

**Oral Cephalosporins**:

Dog: Cephalexin @ 15 mg/kg twice a day; Cephadroxil @ 11-22 mg/kg once or twice a day. The other cephalosporins are administered in dog and cat @ 10-20 mg/kg at 8-12 hr intervals.

Calves: Cefadroxil @ 35 mg/kg; Cefachlor @ 3.5 mg/kg; Cephradine @ 7 mg/kg, all at 12 hr intervals.

**Parenteral Cephalosporins**:

Cephalothin: Dog: 20-40 mg/kg IV at 6-8 hr intervals.

Cafazolin: Dog: 15-30 mg/kg IV at 12 hr intervals; Horse: 15-20 mg/kg IV at 12 hr intervals.

Cefotaxime: Dog: 20-40 mg/kg IM at 8 hr intervals or 50 mg/kg SC at 12 hr intervals; Goat: 50 mg/kg IM at 12 hr intervals; Horse @ 20 mg/kg IM at 8 hr intervals.

Cefoperazone: Dog and Cattle: 30 mg/kg IM at 6-8 hr intervals.

Ceftazidine: Cattle: 20-40 mg/kg IM at 12-24 hr intervals.

Ceftiofur: Cattle: 1.1 mg/kg IM once in a day.

In the treatment of bovine mastitis, the **intramammary cephalosporin-infusion** preparations used are Cefoperazone, Cephalonium, Cefuroxime, Cephacetrile and Cefapirin @ 250 mg/quarter. Cephoxazole @ 250 mg along with 250 mg of procaine penicillin G is also available.

**Side Effects and Toxicity:** Cephalosporins are relatively nontoxic, although some are nephrotoxic (cephaloridine and cephalothin). IM injection is painful (irritant) and injection outside the vein may cause thrombophlebitis. Hypersensitivity (in patients allergic to penicillin), superinfection with *Pseudomonas* or *Candida*. Some cephalosporins cefoperazone, ceftriaxone and moxalactam cause warfarin like hypoprothrombinemia causing prolongation of clotting time and bleeding.

**Cephamycins**

These are closely related to cephalosporins, but have a methoxy group at position 7 of beta-lactam ring of 7-aminocephalosporanic acid nucleus. Cephamycins are also produced by Streptomyces. The common cephamycins are cefmetazole and cefotetan, which are similar in properties to II generation cephalosporins. Moxalactam a synthetic cephamycin is similar in action to III generation cephalosporins.

**Monobactams**

Aztreonam: A beta-lactam antibiotic. Inhibits Gram negative enteric bacilli, *Haemophilus influenzae* and *Pseudomonas*, but not Gram positive cocci and anaerobes. Used in serious hospital acquired infections of uinary, biliary, GI and female genital tract. It can be used in patients allergic to penicillin and cephalosporins.

Dose: Man: 0.5-2 g IM or IV at 6-12 hr intervals.

**Carbapenems**

Imipenem: Extremely potent and broad-spectrum beta-lactam antibiotics effective against Gram positive *Cocci, Enterobacteriaceae, Pseudomonas aeruginosa, Listeria*, anaerobes etc. It is resistant to most beta-lactamases. It is rapidly hydrolysed by the enzyme dehydropeptidase I (found in the brush border of renal tubular cells); therefore, combined with cilastin (inhibitor of dehydropeptidase). It is used in serious hospital acquired infections particularly in immunodepressed patients (Cancer/AIDs).

**2. Aminoglycoside (Aminocyclitol) Antibiotics**

These are a group of natural and semisynthetic antibiotics which contain aminosugars in glycosidic linkage.

**Classification**: Based on antibacterial spectrum:

**Narrow spectrum**: Streptomycin and dihydrostreptomycin. Mainly active against aerobic Gram negative bacteria (*E.coli, Salmonella, Pasteurella spp, Brucella spp*) and also against *Staphylococci, Actinomyces bovis* and *Leptospira spp. Mycobacterium tuberculosis* is sensitive to streptomycin.

**Extended spectrum**: Neomycin, framycetin, paromomycin and kanamycin.They have broader spectra than streptomycin and effective against both aerobic gram-negative bacteria as well as against several Gram positive bacteria. They are clinically most useful against Gram negative infections caused by *E.coli, Salmonella, Klebsiella* and *Enterobacter*.

**Broad spectrum**: Gentamicin, tobramycin, amikacin, sisomicin and netilmicin. Highly effective against a wide variety of aerobic (both Gram positive and Gram negative) bacteria including *Pseudomonas aeruginosa.* Gentamicin is more potent than streptomycin (MIC 4-8 times lower), but it is ineffective against *M.tuberculosis*. Amikacin and netilmicin are resistant to bacterial aminoglycoside inactivating enzymes and therefore have widest spectrum of activity including against organisms resistant to other aminoglycosides.

**Miscellaneous**: Aparamycin and spectinomycin. These drugs are structurally somewhat different from typical aminoglycosides, but have similar antibacterial spectra and mechanism of action.

**Sources**: a) Streptomycin: *Streptomyces griseus;* b) Neomycin: *S. fradiae;* c) Kanamycin: *S. kanamyceticus*; d) Gentamicin: *Micromonospora purpurea;* e) Tobramycin: *S. tenebrarius;* f) Amikacin: Semisynthetic derivative of kanamycin; h) Sisomicin: *Micromonospora inyoensis*; i) Netilmicin: Senmisynthetic derivative of sisomicin; j) Framycetin: *S.lavendulae.*

**Common Properties of Aminoglycosides**:

i) All are used as sulphate salts that are highly water soluble and the solutions are stable.
ii) None is absorbed after oral adm.as they are polycations.
iii) None penetrate the brain or CSF.
iv) All are rapidly excreted unchanged through normal kidney by glomerular filtration.
v) They are exclusively used in the treatment of Gram negative bacterial infections.
vi) All act by interference with the protein synthesis in susceptible bacteria

vii) They are bactericidal and more active at alkaline pH.
viii) Partial cross resistance may be seen among them
ix) They have relatively narrow margin of safety.
x) All share common toxicities (ototoxicity and nephrotoxicity).

**Mechanism of Action**: All the aminoglycoside antibiotics inhibit bacterial protein synthesis. They exert a fast bactericidal action. The antibiotics diffuse across the bacterial membrane and bind to the ribosomal subunits. Streptomycin binds with 30S subunit; whereas, others bind to additional sites on 50S ribosomal subunit as well as 30S-50S interface. The binding interferes with the mRNA codon recognition resulting in misreading of the mRNA code and incorporation of one or more incorrect amino acids into the growing peptide chain or production of peptides of abnormal length. The bactericidal action of these drugs is due to the secondary changes in the integrity of the bacterial cell membrane. Due to incorporation of faulty proteins into the cell membrane it becomes more permeable and as such ions, amino acids and even proteins leak out followed by cell death.

**Pharmacokinetics**: Aminoglycosides are poorly or not absorbed from the GI tract but absorption from IM site is rapid and complete ( peak plasma conc. by 1 hr).They distribute only into the extracellular fluid with minimum penetration to most of the tissues except the kidney (nephrotoxicity)and the endolymph of the internal ear (ototoxicity). They show low tendency to bind with plasma proteins and effective levels are not reached in CSF or milk. These antibiotics are not metabolized in the body of the animals and are mainly eliminated unchanged in urine by glomerular filtration.

**Clinical Uses**: Aminoglycosides are commonly used in several local and systemic infections caused by susceptible aerobic bacteria (particularly Gram negative bacteria).

a. Streptomycin is widely used for the treatment of bovine streptococcal and staphylococcal mastitis (Strepto-penicillin as oily intramammary infusion), pasteurellosis and *E.coli* infection (causing mastitis, metritis, enteritis and septicemia in all species), leptospirosis (for clearance of organism from urine), tuberculosis and vibriosis.
b. Gentamicin is parenterally used in the treatment of Gram negative septicaemia (drug of choice), urinary tract, GI tract, respiratory tract and topically in eye/ear infections.
c. Framycetin rarely used systemically because of ototoxicity and nephrotoxicity but used for the treatment of enteritis and topically for otitis externa in dogs.
d. Netilmicin is resistant to bacterial aminoglycoside inactivating enzymes and thus effective against gentamicin resistant strains.

**Adverse reactions and Toxicity**: The aminoglycosides produce toxic effects which are common to all but the relative intensity may differ. The main toxicities are:

a. **Ototoxicity**: This is the most important dose and duration of treatment related adverse effect. The ototoxicity involves progressive and irreversible damage to and destruction of the sensory cells in the cochlea and vestibular apparatus of the internal ear. Vestibular damage leads to nystagmus, vertigo and ataxia. Cochlear damage cause auditory disturbances which may even lead to deafness. Concomitant administration of other ototoxic drugs potentiates the ototoxicity of aminoglycosides. Cats are particularly sensitive to vestibular toxicity. Streptomycin and gentamicin are more prone to produce vestibular toxicity; whereas, neomycin and amikcain cause mainly cochlear damage. Netilmicin is less ototoxic and therefore preferred for long term use.
b. **Nephrotoxicity**: It is due to damage of kidney tubules and this is more common in patient with pre-existing kidney diseases.Renal damage can be reversed by immediate discontinuation of drugs.
c. **Neuromuscular blockade**: High doses of aminoglycosides may cause neuromuscular blockade (due to chelation of calcium and reduction of ACh release from the motor nerve endings by aminoglycosides) resulting in skeletal muscle paralysis and respiratory arrest which may even lead to death. Neomycin and streptomycin are more prone to cause this toxic effect than kanamycin, gentamicin or amikacin. Tobramycin is least toxic in this respect. The blockade can be partially antagonized by IV calcium gluconate and neostigmine. Neuromuscular blockers should be used cautiously in animals receiving aminoglycoside antibiotics.

d. **Hypersensitivity reactions**: Contact dermatis and sometimes allergic reaction particularly to streptomycin is common.

e. **Rapid IV injection**: At high doses may cause CNS disturbances, even convulsions, respiratory arrest, fall in BP, collapse and death.

**Contraindications and precautions**: To be avoided durig pregnancy (fetal toxicity), along with other ototoxic drugs (high ceiling diuretics, minocycline etc) and with other nephrotoxic drugs (amphotericin B, cephaloridine etc). Neomycin is contraindicated in animals prone to post-perturient hypocalcaemia.

**Dosages of Aminoglycosides**:
Streptomycin and dihydrostreptomycin: Oral: 20 mg/kg 2-3 times in a day; IM: 8-12 mg/kg twice a day; Intramammay @ 100 mg/quarter (in dry cows).
Gentamicin: 3-6 mg/kg IM or SC 2-3 times a day
Kanamycin: 12-15 mg/kg IM or SC twice a day
Amikacin: 5-7.5 mg/kg, IM or SC once or twice daily.
Netilmicin: 3-6 mg/kg, IM or SC once or twice daily.
Neomycin: Oral: 20 mg/kg thrice a day; Intramammary @ 0.5 -1 gm/quarter daily.
**Drug withdrawal time for Aminoglycosde antibiotics**: Oral dosing: 20-30 days; Parenteral: 100-200 days and 2-3 days after intramammary administration (Usually not approved for use in food animals).

**Miscellaneous Aminoglycosides**
**Spectinomycin:** An aminocyclitol antibiotic produced by *Streptomyces spectabilis*. It is active against several Gram positive organisms (frequently used as alternative to Penicillin G), a wide range of Gram negative bacteria and *Mycoplasma* species.It inhibits the protein synthesis in these organisms by binding with 30s ribosomes and produces a bacteriostatic rather than bactericidal effect. It is poorly absorbed from GI tract but rapidly absorbed after IM administration. The antibiotic is mainly used in the treatment of CRD and fowl cholera in poultry, colibacillosis in pigs and poultry and *E.coli* mastitis in cows.
**Dose**: Oral: 20 mg/kg twice daily; IM: 5-10 mg/kg twice daily (Withdrawal periods for pigs: 3 weeks)

**Apramycin:** It is a bactericidal antibiotic, mainly used to control Gram negative infections, especially *E.coli* and *Salmonella* infections in calves and piglets. It is also active against *Proteus, Klebsiella*, T*reponema* and *Mycoplasma* species. It is not absorbed orally but rapidly absorbed parenterally.The drug is contraindicated in cats because of its severe toxic action, but it can be given safely to other animals. It is used in the treatment of colibacillosis and salmonellosis in calves and piglets.
**Dose**: Oral: 20-40 mg/kg, once daily for 5 days for enteric infections; Parenteral: 20 mg/kg twice daily (Withdrawal period after oral use in calves and pigs: 4 weeks).

## 3. Tetracyclines

These are a group of natural and semisynthetic antibiotics having nucleus of four cyclic rings. All are obtained from soil actinomycetes and have nearly similar antimicrobial activity. All are crystalline yellow powder, slightly water soluble but their hydrochloride salts are more soluble and are used ( except doxycycline which is available as hyclate). It contrasted from penicillin G and Streptomycin in being orally active and broad spectrum antibiotic.

**Classification: Based on sources**:
a) Natural: Chlortetracycline (*Streptomyces aureofaciens*), oxytetracycline (*S. rimosus*), demethylchlortetracycline/demeclocycline (a mutant strain of *S. aureofaciens*).
b) Semisynthetic: Tetracycline, methacycline, rolitetracycline, lymecycline, doxycycline and minocycline.

**Based on duration of action**:

a) **Short acting**: Tetracycline, oxytetracycline and chlortetracycline.
b) **Intermediate acting**: Demeclocycline and methacycline.
c) **Long acting**: Doxycycline and minocycline (highly protein bound and slowly excreted).

**Antibacterial spectrum**: All tetracyclines are broad spectrum antibiotics and practically inhibit all types of pathogenic microorganisms except Mycobacteria, fungi and viruses. Tetracyclines are active against both aerobic and anaerobic Gram positive and Gram negative bacteria, *Mycoplasma, Rickettsiae, Chlamidia* and even some protozoa like *Babesia, Theileria, Anaplasma, Coccidia* and *Entamoeba*. Some strains of *E.coli, Klebsiella, Proteus, Psedomonas aeruginosa* and *Corynebacterium* spp.are frequently resistant to tetracyclines. Therapeutically effective level in serum is 0.5 to 4 µg / ml of serum.

**Mechanism of Action**: The tetracyclines are primarily bacteriostatic, but exert bactericidal effect at higher doses. Therefore, a responsive host defense system is essential for their successful use. They inhibit the bacterial protein synthesis by preferential binding with 30 S ribsome in susceptible organisms by preventing the attachment of amino acyl-t-RNA to the acceptor site of mRNA- ribosome complex. As a result peptide chain fails to get elongated.
Tetracyclines concentrate within the susceptible bacterial cells either by a carrier mediated active process or by diffusion (in Gram negative bacteria) through porin channels to produce its action. Doxycycline and minocycline have greatest lipid solubility and enter bacteria by passive diffusion also which make them more potent. The selective toxicity of tetracyclines for the microbes is due to the absence of carrier for active transport of tetracyclines in the host cells and less sensitiveness of host cell protein synthetizing apparatus.
Microbial resistance to tetracyclines is mainly due to decreased penetration of the drug into the previously susceptible organisms (mutation or plasmid mediated).

**Pharmacokinetics**: Tetacyclines are administered orally (mainly to small animals), parenterally (mostly IM and IV) and also topically. Following oral administeration in carnovores the drugs are absorbed rapidly from GIT reaching peak plasma concentration within 2-4 hr which persists for 6-8 hr. Milk and milk products, calcium, magnesium, iron or iron preparations and antacids interfere with the absorption of the tetracyclines in the GI tract due to chelation. The absorption of doxycycline and minocycline is complete and highest in the GI tract and is not interfered with milk and metals because of their high lipid solubility. Some drugs also undergo enterohepatic cycling. Tetracyclines should not be administered orally to ruminants as they are poorly absorbed and cause disruption of ruminal microflora.

In veterinary medicine, specially buffered tetracycline solutions (to avoid irritation) are most commonly administered by IM and sometimes by IV routes. IM dosage gives peak blood levels after 2 hr and maintained for 12-24 hr. Chlortetracycline should not be administered IM because of severe tissue irritation and damage. The long acting tetracyclines are produced by delaying their absorption from IM sites by using a special carrier or increasing magnesium content. Oily preparations, used for SC administration in poultry should not be administered parenterally to mammals.

Tetracyclines are widely and extensively distributed to almost all the body tissues and fluids, particularly after parenteral administration. These drugs undergo chelation with calcium and are deposited irreversibly in growing bones and teeth in young animals. Doxycycline and minocycline readily penetrate tissues and also CSF. Protein binding varies from 30% (oxytetracycline) to 90% (doxycycline).
Tetracyclines undergo limited metabolism in domestic animals except doxycycline and minocycline (partly).They are chiefly excreted by kidney via glomerular filtration and also excreted unchanged in faeces directly or through bile. Most tetracyclines will accumulate if renal function is impaired and increase nephrotoxicity. Doxycycline is an exception as it is largely excreted through the GI tract. They are also secreted in milk. Their minimum therapeutic level is 0.5 to 1 µg per ml serum.

**Clinical uses**:Tetracyclines are used in local infections viz. in mastitis (local + parenteral), coliform-salmonella enteritis, bronchopneumonia in all species, urinary tract infections, metritis, pyodermatitis, cystitis in small animals and specific diseases like actinomycosis, actinobacilosis, keratoconjuntivitis, brucellosis, chlamydiosis, rickettsiosis (especially chlortetracycline), nocardiosis (especially minocycline), borreliosis, ehrlichosis (especially doxycycline), haemobartonellosis, babesiosis, anaplasmosis, theileriasis, amoebiasis, balantidosis, leptospirosis, pasteurellosis (transit fever, HS, fowl cholera), bacterial diseases of poultry (blue comb in turkey, CRD, contagious catarrh), to check secondary bacterial infection in viral infections.

**Adverse Reactions and Toxicity**:

a) Alteration in microflora in rumen or intestines following oral use leads to digestive disturbances and ruminal stasis and decrease in synthesis and availability of vitamin B and K particularly in monogastric animals.
b) Superinfections by fungi, yeasts and resistant bacteria may cause severe or fatal diarrhea (horse) following oarl or parenteral administration.
c) Tetracyclines are deposited in growing teeth and bones and should not be used in growing animals because they cause yellowish and later brownish discoloration of teeth and supress bone growth.
d) Tetracycline should not be used with immunization programmes (as they cause immunosuppression).
e) Intramammary infusion of chlortetracycline is contraindicated in dry cows (cause severe tissue irritation and subsequent fibrosis) and if infused, cows may fail to lactate after parturition (due to teat and udder tissue damage).
f) Intraarticular injections of tetracyclines are contraindicated (cause severe irritation and inflammation).
g) If administered by rapid IV injection, hypotension and acute collapse may occur in cattle and horses due to chelation of blood $Ca^{++}$ and this can be avoided by slow infusion of the drug or pretreatment with IV calcium gluconate.
h) Tetracyclines in high doses produce hepatotoxicity particularly in pregnant animals or those having renal abnormality.
i) All tetracyclines in high doses are potentially nephrotoxic (due to decrease in host protein synthesis and anti-anabolic effect) except doxycycline and are contraindicated in renal insufficiency.
j) Phototoxic dermatitis is most common with demeclocycline and doxycycline in man which is rare in animals. Hypersensitivity is rare.
k) In human ingestion of outdated tetracyclines produces a syndrome characterized by aminoaciduria, glycosuria, pyuria and polydypsia due to proximal convoluted tubular damage (Fanconi syndrome).
l) Demeclocycline induces diuresis (ADH antagonism).

**Precautions**: Contraindicated in pregnant, lactating and young animals. Must be cautiously used in animals with renal and hepatic dysfunctions. Injectable tetracyclines should never be mixed with penicillin (precipitation-inactivation occurs).

**Dosage**:

Tetracycline and oxytetracycline: Dog & Cat: 20 mg/kg orally at 12 hr intervals; 7-10 mg/kg/day IM or IV once a day.
Oxytetracycline: Calf, foal, lamb & pig: 10-20 mg/kg orally at 12 hr intervals; Horse, foal, cattle, calf, sheep, lamb & pig: 5-10 mg/kg IM orIV once a day.
Doxycycline: Small animals: 5-10 mg/kg orally once a day; 5 mg/kg IM or IV once a day.
Rolitetracycline: Cattle: 2 mg/kg IV once a day.
**Withdrawal periods**: Oxytetracycline: Cattle & Pig: 22 days; Poultry: 5 days; Oxytetracycline (long acting): cattle-28 days; Chlortetracycline: Cattle: 10 days; Pig: 7 days; Oxytetracyclines are not to be used in lactating cows.

## 4. Chloramphenicol and Congeners

The isolation of chloramphenicol was reported by Ehrlich, Burkholder and coworkers in the year 1947. It was naturally obtained from *Streptomyces venezuelae* and was the first antibiotic to be manufactured synthetically for clinical use.

**Chemistry**: It is a yellowish-white crystalline, intensely bitter solid. Its aqueous solution is stable, withstands boiling, but needs protection from light. It has a nitrobenzene substitution, which is responsible for its antimicrobial activity.

**Chloramphenicol**: It is a highly effective broad spectrum antibiotic. But this drug causes severe blood dyscracias in human so carefully used in pet animals and not approved for use in food animals in many countries. Two chloramphenicol congeners viz. thiamphenicol and florfenicol (less toxic to bone marrow) have been developed.

**Thiamphenicol**: Is produced by replacing the nitrophenolic group of chloramphenicol by a methylsulphonyl group. It is less effective but safer than chloramphenicol.

**Florfenicol**: It is a fluorinated derivative of thiamphenicol, more effective than chloramphenicol, resists bacterial destruction and approved for use in cattle.

**Antimicrobial spectrum**: It is a broad spectrum antibiotic effective against both Gram positive and Gram-negative bacteria and several anaerobes (*Bacteroides fragilis*), as well as *Rickettsia, Chlamidia* and *Mycoplasma* like tetracycline. It has special efficacy against *Salmonella* including *S. typhi*, but less action on Gram positive cocci. Like tetracycline it is inactive against *Mycobacteria*, *Pseudomonas*, many *Proteus* spp, viruses and fungi. Florfenicol also has broad antimicrobial spectrum. Bacterial resistance is due to synthesis of chloramphenicol acetyltransferase (plasmid mediated).

**Mechanism of Action**: Chloramphenicol and its congeners bind to the 50S subunit of the bacterial ribosome (at the same site as do erythromycin and clindamycin) and also interfere with the bacterial peptidyl transferase activity. These results in the inhibition of microbial protein synthesis due to interference with the transfer of elongated peptide chain to the newly attached aminoacyl-tRNA at the m-RNA-ribosome complex (i.e. transpeptidation). At high doses it also inhibits mammalian mitochondrial protein synthesis particularly in bone marrow.

**Pharmacokinetics**: Chloramphenicol palmitate, given orally, is rapidly and completely absorbed in monogastric animals and reaches peak plasma concentration within two hours. Florfenicol is also rapidly absorbed orally, although milk interferes with its absorbption. In ruminants, the chloramphenicol is orally ineffective as it is readily inactivated (reduced to inactive aminochloramphenicol) by the ruminal microflora and therefore given only parenterally. Chloramphenicol sodium succinate administered by IM or IV route is hydrolysed into active free chloramphenicol. In plasma, 40-50% reversibly binds to the plasma protein and the free fraction is widely distributed throughout the tissues and body fluids including CSF (florfenicol less), milk, aqueous humor and placental fluid. Its unique property is the ability to attain high conccentration in CSF (40-60% of plasma concentration), even in absence of meningeal inflammation. Chloramphenicol is mainly inactivated in liver by conjugation with glucuronic acid and also reduced to inactive amines and the metabolites are excreted in urine by active tubular secretion. Only 10% is excreted as free drug in urine by glomerular filtration.

**Therapeutic uses**: The use of chloramphenicol should be reserved for serious infections in which the benefit of the drug is greater than the risk of toxicity. It is used for both local and systemic infections in animals: Drug of choice in *Salmonella* and *Bacteroides* septicaemia, also used in bacterial meningoencephalitis, brain abscess, ophthalmitis, mastitis (Intramammarily and/or parenterally), intraocular infections, equine dermatophilus infection, urinary tract infections (haematogenus delivery), superficial skin and eye infections and in otitis externa (as 1% topical preparation ).

In human it is effective in typhoid and paratyphoid fever but ciprofloxacin or amoxicillin and cotrimoxazole (in adult) or cefixime/cefoperazone/ceftriaxone (in children) are similarly effective and less toxic drugs.

**Toxicity**: Chloramphenicol in man (but not florfenicol) produces two types syndrome related to bone marrow deppression.

a. **Non regenerative anaemia**: Such blood dyscrsias may also be seen in susceptible neonatal animals treated with adult doses of chloramphenicol. This is the direct toxic effect of drug related to the interference with mRNA and protein synthesis in rapidly multiplying bone marrow cells.

b. **Reversible aplastic anaemia**: It is sometimes seen in dogs and cats, much more serious and related to idiosyncratic reaction. Thiamphencol and florfenicol, without the nitro group, do not produce aplastic anaemia.

c. **Gray baby syndrome**: Chloramphenicol should be used with great care in newborns because inadequate inactivation and excretion of the drug result in such toxic syndrome – vomiting, flaccidity, hypothermia, and an ashen grey cyanosis followed by CV collapse and death.

d. Oral administration of chloramphenicol in monogastric animals causes GI disturbances.

e. Hypersensitivity reactions to the antibiotic are uncommon. The antibiotic causes immunosuppression so animal should not be vaccinated while being treated with chloramphenicol. In large animal rapid IV injection of preparations containing propylene glycol may results in haemolysis, collapse and death.

**Drug interactions**: Chloramphenicol (a potent microsomal enzyme inhibitor) inhibits the metabolism of many other drugs like phenytoin, barbiturates, primidone, local anaesthetics and thereby either prolong their action or precipitate toxicity. On the other hand, phenobarbitone and phenytoin enhance chloramphenicol metabolism, reduce therapeutic concentration and cause failure of chemotherapy. It should not be combined with bactericidal drugs and drugs that bind to 50S ribosomal subunit (macrolides and lincosamides)

**Dosage**: Chloramphenicol: Oral administration (as capsule or as palmitate suspension): Calves & foals: 0.5 gm, 2-3 times daily; Piglets & lambs: 0.25g, 2-3 times daily; Dogs: 50-150 mg/kg, in three divided doses.
Parenteral: Chloramphenicol sodium succinate 10% for IV and 40% for IM injection: Large animals: 2-4 mg/kg; Sheep, goat, pigs, foals and calves: 4-10 mg/kg.
Florfenicol: Cattle: 20 mg/kg, IM, at 48 hr intervals.

**Withdrawal period:** Chloramphenicol has not been approved for use in food producing animals and if used its minimum withdrawal time is 2 weeks. Withdrawal time for florfenicol is 28 days. Florfenicol should not be used in dairy cattle. Its withdrawal period for meat is 28 days.

## 5. Macrolide Antibiotics

Macrolide antibiotics contain many membered lactone ring to which one or more deoxy sugars are attached. The clinically important members of this group are:
Class I: Erythromycin, oleandomycin and troleandomycin. They have a 14 membered ring.
Class II: Spiramycin, josamycin, tilmicosin and tylosin.These are having a16 membered ring.
Recently some newer semisynthetic macrolides (Roxithromycin, clarithromycin and azithromycin) have been developed and used in man and small animals as an alternative to erythromycin.

### Erythromycin

It is the prototype drug of this group. **Erythromycin** was obtained from *Streptomyces erythreus* in 1952.

**Antibacterial spectrum**: Macrolides are mainly effective against most aerobic and anaerobic Gram positive bacteria. In general, macrolides are narrow spectrum antibiotics and not effective against Gram negative bacteria although some strains of *Pasteurella, Haemophilus* and *Neisseria* spp are moderately sensitive. They are also active against *Mycoplasma, Chlamydia* and *Ricketssiae* spp, but not against protozoa and fungi. Tilmicosin is a broad spectrum macrolide and has exceptionally high activity against *Pasteurella haemolytica* and *P. multocida*. Some of the members are also active against *Mycobacterium* and are used in the treatment of tuberculosis in man.

**Mechanism of action**: All the macrolides are bacteriostatic antibiotic and have similar mechanism of action.They act by inhibiting the bacterial protein synthesis in susceptible organisms. They bind with the 50S bacterial ribosomal subunit and interfere with translocation of the nascent elongated peptide chain at the acceptor (A) site back to the peptidyl (P) site required to make the A site available for next aminoacyl-tRNA attachment. This results in failure of ribosome to move along the mRNA to expose the next codon, premature termination of peptide chain and ultimately suppression of protein synthesis.
Macrolides should not be administered with chloramphenicol and lincosamides as they may compete for binding to the same 50 S ribosomal subunit.
Resistance to macrolides in Gram positive bacteria may occur due to change in bacterial ribosomal structure or loss of macrolide affinity.
**Pharmacokinetics and Administration**: Erythromycin base as such is destroyed by gastric acid. Macrolides are readily absorbed from the GI tract if it is administered orally as acid resistant salts (stearate, estolate, lactobionate) or as tablets with acid resistant coating. The absorption from rumen is very slow and unreliable.Erythromycin and tylosin are rapidly absorbed following IM administration. Tilmicosin is administered SC. Macrolides are widely distributed into the most tissues (particularly in lungs) and fluids but not the CSF unless the membranes are inflammed. Diffusion also occurs through the peritoneal and pleural cavities and placenta. The drugs undergo 70-80% plasma protein binding.They concentrate in bile and milk. Following oral administration they are mainly metabolized in liver, excreted mainly in bile and undergo enterohepatic cycling. After parenteral administration the drugs are mainly excreted through urine.
**Side Effects and Toxicity**: In general, macrolides are least toxic antibiotic but tilmicosin is comparatively toxic.They are irritants and may cause pain and swelling at the site of injections. Erythromycin estolate salt is particularly hepatotoxic and may cause cholestatic jaundice. Hypersensitivity reactions or skin reactions may occasionally be seen. High doses may cause severe GI disturbances (vomiting, diarrhea, oedema of GI mucosa etc). Horses are particularly highly sensitive and may suffer from serious and even fatal GI disturbances.Tylosin in dogs causes tachycardia, fibrillation and myocardial ischaemia. Tilmicosin is cardiotoxic and causes tachycardia and decrease the cardiac contractility and it is contraindicated in pigs.
**Clinical Uses**: Macrolides are used as an alternative to Penicillin G in Gram positive infections (particularly in patient allergic to penicillin), in respiratory tract infections, in the treatment of atypical pneumonia caused by Mycoplasma pneumoniae, bronchopneumonia, bacterial enteritis, urinary tract infections, bacterial pyodermatitis, arthritis, mastitis, metritis and CRD in poultry.
**Dosage**: Erythromycin: Dog & cat: Oral: 15 mg/kg three times a day; Cattle, horse, dog, cat, pig: Parenteral (IM): Erythromycin lactobionate: 8-15 mg/kg once or twice a day. Intramammary @ 200 mg/quarter thrice a day; Poultry: 0.10-0.25 gm/L in drinking water for 3 days.
The **withdrawal period** for meat: Cattle: 14 days; Pigs: 7 days. Milk discard time: Cattle: 3 days
**Oleandomycin and Troleandomycin**: Oleandomycin is obtained from *Streptomyces antibioticus.* Troleandomycin is a derivative of oleandomycin. Both drugs possess erythromycin like antibacterial spectrum and have special activity against Staphylococci and Streptococci.
**Dose**: Either drug is adm. orally @ 1.2-2.2 mg/kg at 6 hour intervals. In veterinary medicine, they are used in the treatment of staphylococcal and streptococcal mastitis. Combination of oxytetracycline and oleandomycin in 2:1 ratio administered by IM or IV route strengthen the activity against Gram positive organisms.

**Spiramycin:** Source: A strain of *Streptomyces ambofaciens*. Its antibacterial activity is also similar to erythromycin and oleandomycin. It attains a high concentration in body fluids (particularly pleural and peritoneal fluids); thus it is the drug of choice in the treatment of contagious bovine pleuropneumonia (@ 25 mg/kg, IM, 3 injections at 48 hr intervals). It is also used for the treatment of toxoplasmosis in ewes (100 mg/kg, orally), ovine rickettsial keratoconjuntivitis (20-30 mg/kg, IM), CRD in poultry and swine dysentery caused by *Treponema hyodysentriae.*

**Tylosin**: Source: A strain of *Streptomyces fradiae*. Its antibacterial spectrum is similar to erythromycin.
**Administration**: Tylosin tartrate is administered in drinking water to chickens, turkeys and pigs and also SC to chickens. Tylosin phosphate is adm to pigs in feed. Tylosin base is administered IM to cattle, calves, pigs, dogs and cats.The clinical application of tylosin is as follows:
Cattle: Pneumonia, foot rot and metritis @10-20 mg/kg IM once or twice a day.
Pigs: Swine dysentery and pneumonia @ 5-10 mg/kg IM once or twice a day; 7-10 mg/kg orally thrice a day.
Dogs and cats: Respiratoty and urinary tract infections, otitis externa, metritis, leptospirosis and to check secondary bacterial infections in viral diseases @ 10 mg/kg IM twice a day.
Poultry: CRD in poultry and infectious sinusitis in turkeys @ 0.5g/L of drinking water orally or @ 1ml/kg SC.
Tylosin should not be given to birds producing eggs for human consumption.
Withdrawal period for meat: Cattle: 14 days; Pigs: 21 days; Milk discard time: Cattle: 4 days

**Tilmicosin**: It is mainly used in the treatment of bovine respiratory diseases associated with *Pasteurella haemolytica*. Dose: Cattle: 10 mg/kg SC, single injection (IV injection may cause fatality). Withdrawal period for meat: Cattle: 28 days; Pigs: 21 days; Milk discard time: Cattle: 0 days

**Newer Macrolides**: To overcome the limitations of erythromycin viz. narrow spectrum activity, poor tissue penetration, gastric acid lability, low oral bioavailability and short half life some semisynthetic macrolides like **roxithromycin, clarithromycin and azithromycin** have been developed; their antibacterial spectrum is similar to that of erythromycin and some are more active against *Mycoplasma* and *Chlamydia*. They are mainly used in man and small animals as an alternative to erythromycin for respiratoty tract infection, pneumonia, skin, soft tissue and genital tract infections.

## 6. Lincosamides

These antibiotics closely resemble macrolide antibiotics in their antibacterial spectrum, mechanism of action and clinical application. The most important members of this group are lincomycin and clindamycin.

### Lincomycin

It is produced by *Streptomyces lincolnensis*. The drug is active against Gram positive bacteria including penicillinase producing *Staphylococci, Streptococci, Clostridium tetani, Cl. perfringens, Erysipelothrix, Actinomycetes, Nocrdia* and certain strains of *Mycoplasma pneumoniae*. Its most distinctive feature is its activity against a variety of anaerobes (*Bacteroides fragilis*). However, aerobic Gram negative bacilli are not affected. Lincosamides can be administered orally, IM or IV. Lincomycin is readily absorbed orally and completely absorbed from IM sites. The drug is widely distributed in the body including skeletal and soft tissues but cannot penetrate the blood brain barrier. It is largely metabolized in liver and the metabolites are excreted in urine and bile.
**Clinical Uses**: Because of serious toxic effect its use is restricted in infections caused by susceptible Gram positive bacteria, particularly *Staphylococci* and *Streptococci* and for those by anaerobic pathogens.The drug is used in respiratory, skeletal, skin, joint and adjoining tissue infections in dogs and cats. It is also used to treat infectious arthritis in pigs (due to *Streptococci, Staphylococci, Erysipelothrix* and *Mycoplasma*) and pneumonia in pigs due to *Mycoplasma*.
**Side Effects and Toxicity**: These drugs have no serious organ toxicity. GI disturbances may occur. The major problem in man is superinfection diarrhoea and pseudomembranous colitis (treated by vancomycin) caused by a toxin produced by *Clostridium difficile*. Hypersensitivity reaction and skeletal muscle paralysis may also occur. Lincosamides are contraindicated in horses (because sevre and fatal colitis may develop) and in neonates (due to limited ability to metabolize the drugs).
**Dosage**: Dog & cat: Oral: 20 mg/kg orally once or twice a day; IM: 10 mg/kg twice daily; Cattle & pigs: IM: 10 mg/kg twice daily.

**Clindamycin**

It is a semisynthetic derivative of lincomycin and differs chemically from lincomycin by substitution of a chloride atom for a hydroxyl group. It is more potent than the parent compound. Its absorption is better than lincomycin and has reduced the incidence of adverse effect than lincomycin. The antibacterial spectrum and clinical application is similar to lincomycin. It has replaced lincomycin for anaerobic, skeletal, soft tissues and skin infections.

Dose: Dogs: 5-10 mg/kg orally twice daily.

The bacteria may develop cross resistance between macrolides, lincosamides and other antibiotics which have common mechanism of antibacterial action.

**7. Quinolones and Fluoroquinolones**

These are entirely synthetic antimicrobials having quinolone structure. They are becoming more important in veterinary medicine.The various clinically important compounds under this group are divided into two classes:

I. **First generation** (Original quinolones): Nalidixic acid, oxolinic acid, cinoxacin and resoxacin: These are primarily active aginst Gram negative bacteria specially coliforms but not against *Pseudomonas*. Their use is restricted only for the treatment of urinary and GI tract infections because of their CNS toxicity, low potency, moderate blood and tissue levels, limited spectrum and high incidence of bacterial resistance.

II. **Second generation** (**Fluoroquinolones**: FQs): Ciprofloxacin, enrofloxacin, norfloxacin, difloxacin, ofloxacin, pefloxacin, danofloxacin, marbofloxacin and flumequine: Addition of one or fluorine atoms and other substitutions in the quinolone molecule yield fluoroquinolones with enhanced antibacterial potency, expanded spectrum, better tissue penetrability, reduced toxicity and retard development of bacterial resistance.

Fluoroquinolones are highly active against a broad range of aerobic Gram negative and Gram positive bacteria. The most susceptible ones are the aerobic Gram negative bacilli (MIC < 0.1 ug/ ml), especially the Enterobacteriaceae and Neisseria.They are also effective against several intracellular pathogens (*Brucella* spp) and have significant activity against *Mycoplasma* and *Chlamydia* spp. Some are also active against *Mycobacteria* (ciprofloxacin, ofloxacin).Their notable microbiological features are: high potency and rapid bactericidal activity particularly against Gram negative infections including *Pseudomonas*, no activity against anaerobes, low incidence of resistance, active against beta lactam and aminoglycoside resistant bacteria and less activity at acidic pH.

**Mechanism of Action**: The separation of double stranded DNA is must for DNA replication or transcription. However, anything that separates the strands results in 'overwinding' or 'excessive positive supercoiling of the DNA in front of the point of separation and damage of DNA. To prevent this, the bacterial enzyme DNA gyrase nicks the double stranded DNA and introduces negative supercoils and then reseals nicked ends. The DNA gyrase enzyme consists of two A subunits and two B subunits. During DNA transcription or replication the A subunit nicks the DNA, B subunits introduces a negative supercoil and then A subunit again reseals the strands.

Fluoroquinolones bind to A subunit of DNA gyrase enzyme with high affinity, inhibit it, interfere with DNA replication or transcription and ultimately cause DNA damage. The bactericidal action results from digestion of DNA by exonucleases whose production is signaled by damaged DNA.

The mammalian cells possess an enzyme topoisomerase II (analogus to bacterial DNA gyrase which also removes positive supercoils) which has very low affinity for fluoroquinolones and hence are less toxic to the host cells.

Quinolones are synergistic with beta-lactams, aminoglycosides and metronidazole.

**Pharmacokinetics**: Quinolones are commonly administered orally, IM, SC, IV and also topically. Oral bioavailability in monogastric animals is about 80% (food delays absorbtion) for most quinolones but in

adult ruminant it is low. FQs have high tissue penetrability and wide distribution to the tissues and fluids. Some members also cross the blood- brain barrier and attain high concentration in CSF (pefloxacin). Some are eliminated unchanged (ofloxacin) and some are metabolized in liver and the metabolites (sometimes active; enrofloxacin to ciprofloxacin) undergo glucuronidation and are mainly excreted by kidneys, both by glomerular filtration and tubular secretion. In some cases (ciprofloxacin, pefloxacin) the parent drug as well as metabolites are mainly eliminated in bile. Quinolones also appear in milk when administered to lactating animals. Nitrofurantoin (bacteriostatic) interferes with efficacy of quinolones (bactericidal).

**Clinical Uses**: Because of broad spectrum of activity, oral as well as parenteral efficacy, high tissue penetrability and good tolerability. FQs are extensively used for blind therapy, but they should not be used for minor infections or where Gram positive organisms are primarily suspected. In severe infections, the treatment should be started parenterally. They are particularly good for deep seated infections and for intracellular pathogens. They are used in Gram negative septicaemias; respiratory tract, GI tract, urinary tract, skin and eye infections; also in meningoencephalitis, bacterial prostitis, osteomyelitis, arthritis and mastitis.
In human, some members are also used in the treatment of typhoid (ciprofloxacin; drug of choice) and tuberculosis.

**Doses of Fluoroquinolones**:
Norfloxacin: Dog & Cat: 10-20 mg/kg, orally twice a day.
Ciprofloxacin: Dog: 5-15 mg/kg, orally twice a day.
Enrofloxacin: Dog & Cat: 5 mg/kg orally, once a day, 2.5 mg/kg SC once followed by oral dosage; Poultry: 50 ppm in water
Cattle, Calves & Pig: 2.5-5 mg/kg im or sc, once in a day; Preruminant calves: 2.5-5 mg/kg orally
Marbofloxacin: Cat & Dog: 2.5-5 mg/kg orally, once in a day.
Orbifloxacin: Cat & Dog: 2.5-7.5 mg/kg orally, once in a day.
**Toxicity of Quinolones**: GI disturbances (vomiting, diarrhea etc), neurotoxicity (convulsions, GABA antagonism) at high doses. Cause embryotoxicity in pregnant animals and photosensitization and allergic/hypersensitive reactions in some cases. Fluoroquinolones are relatively safer than older quinolones. FQs cause arthopathic toxicity (erosion of cartilage in weight bearing joint). Dogs are the most susceptible species (mainly in pups/growing dogs), but also occurs in young foals.

## 8. Antitubercular Drugs

These drugs are categorized into two classes depending upon the choice of drug based on the sensitivity of tubercule bacilli.
**First Line Drugs**: Streptomycin (S), isoniazid/isonicotinic acid hydrazide (INH or H), rifampicin (R), ethambutol (E), pyrazinamide (PZ) and thiacetazone (T). Paraaminosaliclic acid (PASA) is also considered as a fist line drug. These have high antitubercular efficacy and low toxicity.
**Second Line Drugs**: Capreomycin (A), cycloserine (C), kanamycin (K) and ethionamde (Et). These have low antiTB efficacy, but relatively high toxicity.
Some clinicians categorize the above drugs as:
**Standard Drugs**: INH or H, R, S, PZ, E and T
**Reserve Drugs**: A, K, Et and C
Fluoroquinolones are also used under reserve category antiTB drugs.
Basing on the Antibacterial Action:
**Bactericidal**: INH or H, R, S, PZ, A, K, C and fluoroquinolones.
**Bacteriostatic**: E, T, Et and PASA
Treatment of TB includes use of combination therapy; to avoid emergence of resistance in tubercule bacilli. In general the first-line (standard) drugs are to be used. The second-line (rsserve) drugs are to be considered when the bacilli become resistant to first-line drugs or when the first-line drugs are to be discontinued due to appearance of adverse reactions. The effective antitubercular combinations include:

1. **Starting Phase**: INH (H), R, PZ and E or S: Daily dosing for 2-3 months.
2. **Continuation Phase**: HR or HE: Daily dosing for about 6 months.

Thus antiTB therapy extends up to a total duration of 8 or 9 months.
The dosage of antiTB drugs in man (mg/kg/day): Isoniazid: 5; Rifampicin: 10; Pyrazinamide: 25; Ethambutol and Streptomycin: 15.

**Isoniazid** is chemically related to MAO inhibitor iproniazid. It is well absorbed from GIT, easily penetrates into caseous tubercule lesions and also readily taken up by TB bacilli; exerts bactericidal effect by inhibiting the synthesis of mycolic acids (essential cell wall constituents in *Mycobacteriun*) and also causing damage to cell membrane by inhibiting phospholipids synthesis. Its prolonged use may cause neurotoxicity (deficiency of pyridoxine due to formation of pyridoxal-hydrazone complex). It has no action on other bacteria.
**Ethionamde** is chemically related o INH (H).
**Ethambutol** (d-Ethambutol) may also act through inhibition of mycolic acid synthesis and cell wall formation; ineffective against other bacteria. It readily enters into RBC, where it serves as store depot.
**Pyrazanamide** is chemically related to nicotinamde and thiosemicarbazones. It is ineffective against bovine TB bacilli. It's MOA in not known.
**Thiacetazone** is derivative of thiosemicarbazone.
**Rifampicin** is a semisynthetic derivative of rifamycin B (*Streptomyces mediterranei*); acts by inhibiting protein synthesis in mycobacteria by inactivating DNA-dependent RNA polymerase. One of the most effective antiTB antibiotics; also effective against many other Gram negative or Gram positive bacteria, including *Mycobacterium laprae*. It imparts orange color to saliva, sputum, tears and sweat.
**Capreomycin** is a peptide antibiotic (*Streptomyces capreolus*). Like streptomycin it causes renal damage and injury to VIII cranial nerve (deafness and ataxia); not to be combined with S or K (synergistic toxicity).
**Cycloserine** A broad spectrum antibiotic also effective against many other bacteria. Being an analog of D-alanine inhibits bacterial cell wall formation by preventing d-ala-d-ala dipeptide synthesis required for formation of N-AMA pentapeptide (peptidoglycon).
**Kanamycin** (*Streptomyces kanamyceticus*); should not be combined with S or A (synergistic toxicity).
**Paraaminosalicylic acid** (PASA) exerts anti PABA activity like sulfonamides; has no antipyretic or analgesic or anti-inflammatory action of salicylic acid.
Fluoroquinolones such as ciprofloxacin, ofloxacin and sparfloxacin and newer macrolides like azythromycin and clarithromycin are also found to be effective against TB bacilli; these drugs can be considered as second-line or reserve category.

## 9. Miscellaneous Antibacterial Agents

**Polymyxins**: Polymyxin B and polymyxin E (colistin) are two clinically important polypeptide antibiotics obtained from *Bacillus polymyxa* and *Bacillus colistinus* respectively. Both the drugs are rapidly bactericidal, narrow spectrum antibiotics, highly active against Gram negative bacteria such as *E.coli, Salmonella* spp. and *Pseudomonas aeruginosa*. They are ineffective against Gram positive bacteria. The polymyxins have a detergent like action on the bacterial cell membrane. They bind with bacterial cell membrane phospholipids with high affinity, distort it. As a result ions, amino acids etc leak out and bacterial cells die.They are neither absorbed topically nor orally and do not penetrate blood brain barrier. For systemic effect they (colistin sodium methanesulphonate) are administered parenterally. Systemically rarely used due to serious toxicity (nephrotoxicity, neurotoxicity and neuromuscular blockade) and only used in life threatening infections caused by Gram negative bacilli or *Pseudomonas*. Orally it is used in Gram negative enteritis in calves and pigs, topically in skin infections (along with neomycin or bacitracin), otitis externa (with oxytetracycline), in bovine mastitis (with oxytetracycline for *Klebsiella* spp) and as semen additive (in bull semen containing *Pseudomonas* organism) @50 u/ml diluent.
Dosage: Oral: 20,000 units/kg, twice daily; IM: 5,000 units/kg, twice daily; Intramammary infusion: 50,000-100000 units; Intrauterine (cattle): 100000 units.

**Bacitracin**: It is another polypeptide antibiotic obtained from *Bacillus subtilis*.Its antibacterial spectrum is similar to penicillin G and is mostly limited to Gram positive bacteria and spirochaetes. It is a bactericidal drug and acts by inhibiting the formation of bacterial cell wall peptidoglycan. It binds with the pyrophosphate lipid carrier and inhibits the dephosphorylation reaction required for regeneration of the lipid carrier. It also increases the fluxes of ions by binding to the bacterial cell membrane.The drug is not absorbed from the GI tract and is not used parenterally because of its pronounced nephrotoxicity. It may cause hypersensitivity reactions. Bacitracin is mainly used for topical infections (skin, eye, ear) especially against *Staphylococcus* in combination with neomycin or polymyxins, as an alternative to vancomycin in antibiotic induced pseudomembranous enterocolitis, in prevention and treatment of enteritis caused by *C. perfringens* in pigs and necrotic enteris in poultry. Zinc-bacitracin is used as a growth promoter in poultry, cattle and swine.

**Vancomycin**: It is a glycopeptide antibiotic produced by *Streptomyces orientalis*. It is bactericidal against many Gram positive organisms.Vancomycin acts by inhibiting the synthesis of cell wall peptidglycan. It binds with the d-alanyl-d-alanine terminal of muramyl dipeptide and inhibits the release of building block unit from the lipid carrier and thus prevents its addition to the growing end of the peptidoglycan.The drug is used as a substitute of penicillin in patients allergic to penicillins, parenterally in serious methicillin resistant *Staphylococcal* infection, orally to treat antibiotic induced pseudomembranous enterocolitis caused by Clostridium difficile cytotoxin and topically in skin infections along with polymyxin. The common toxicities are hypersensitivity, ototoxicity and nephrotoxicity.

**Tyrothricin**: It is a mixture of gramocidin and tyrocidine, obtained from *Bacillus brevis,'* mainly active against Gram positive bacteria, including *Streptococci* and *Staphylococci*. It acts on the cell membrane and causes leakage and also uncouples oxidative phosphorylation in the bacteria. The drug is not absorbed orally, is too toxic for systemic use and causes haemolysis.It is used in bovine mastitis during dry period (as intramammary infusion), to treat metritis (by intrauterine infusion) and topically for skin (0.5mg/g cream) and ear infections (as 0.05% solution). It does not cause hypersensitivity reactions.

**Virginiamycin**: It is an antibiotic produced by *Streptomyces virginiae* and used in the treatment and control of dysentery in piglets as feed additive @ 100 g/ 900kg feed for 2 weeks and @ 50gm/900kg feed thereafter. It has also growth promoting potentiality in pigs like salinomycin.

**Tiamulin**: Tiamulin is a derivative of diterpine antibiotic pleuromutilin, obtained from *Pleurotus mutilis*. It is a bacteriostatic drug active against Gram positive bacteria, mycoplasmas and anaerobes including Treponema hyodysenteriae. It acts through inhibition of protein synthesis by binding to the 50S subunit of the bacterial ribosome. The drug is well absorbed orally. It is used for the treatment of enzootic pneumonia of swine (@15 mg/kg IM, an oil injection) and pneumonia of calves caused by *Mycoplasma* (@ 20 mg/kg, IM), in swine dysentery caused by *T.hyodysenteriae* (10 mg/kg, IM, an oil injection)and mycoplasmal arthritis in pigs. Tiamulin hydrogen fumerate is given orally in food or drinking water @ 8.8 mg/kg/day to control mycoplasma infections in pigs and poultry. In poultry, it interferes with monensin and salinomycin metabolism. So, if the drugs are fed together, they become toxic (potentiation of ionophore myotoxicity).

**Novobiocin**: It is obtained biosynthetically from two actinomycetes viz. *Streptomyces niveus and S. spheroides*. It is a narrow spectrum antibiotic, mainly bacteriostatic and cidal at high conentrations. It is mainly active against Gram positive bacteria and some strains of *Proteus, Pseudomonas* and *Pasteurella multocida*. Novobiocin acts by spincer attack both by interfering the bacterial cell membrane permeability as well as by inhibiting cell wall synthesis.It is synergistic with tetracyclines. It is used mainly in combination with penicillin and other drugs for the treatment of mastitis in bovine (sodium novobiocin intramammary injection @ 250 mg/ infected quarter). Though it has good efficacy against anthrax, various *Streptococcal* and *Staphylococcal* infections in man and animals but not used because of its frequent and serious adverse effects (severe GI disturbances, allergy and blood dyscrasias).

**Rifamycins**: The rifamycins are obtained from *Streptomyces mediterranei*. They are active against Gram positive organisms (notably, even against intraleucocytic *Staphylococci*), a few Gram negative organisms, *Mycobacteria*, some anaerobes, *Chlamydia* and also have antiviral activity at high concentration. As they can readily penetrate the tissues and cells, they are particularly effective against intracellular as well as extracellular organisms. Rifamycins are bactericidal and have unique mode of action. They prevent the DNA dependent RNA synthesis in microorganisms by inhibiting bacterial DNA-dependent RNA polymerase enzyme. The semisynthetic derivatives of rifamycins are rifamycin SV (used parenterally in man for the treatment of cholecystitis as it is largely excreted in bile) and rifampin or rifampicin (primarily used in man for the treatment of tuberculosis mostly in combination with isonazid, in leprosy and in foals to control pneumonia caused by *Rhodococcus* equi). Rifampin can be administered by oral, IM and IV routes and it is readily and complety absorbed orally (peak levels in 2-4 hr). It is widely distributed in the body because of its high lipid solubility and also penetrates placenta and meninges. It is metabolized in liver to active metabolite which is excreted mainly in bile (also undergoes enterohepatic cycling), some also in urine. The drug is a microsomal enzyme inducer and enhances metabolism of its own and other drugs. Rifampin is well tolerated and produces a few adverse effects like hepatitis and jaundice in man, hypersensitivity reactions, GI disturbances, immunosuppression and red-orange colored urine, feces and other secretions. The dosage of rifampin in horses is 10-25 mg/kg, orally or parenterally.

**Methenamine (Hexamine)**: It is inactive as such, but decomposes in acidic urine to formaldehyde which provides antibacterial activity.It may be bactericidal or static depending on the concentration of formaldehyde. Acidic urine is essential for its action, so some organic acids like ascorbic or mandelic acid are frequently administered to carnivores to produce acid urine. It is available as methenamine mandelate that combines the antibacterial action of methenamine and mandelic acid. It is used as a urinary antiseptic in chronic, resistant type of urinary tract infections in dogs and cats, not involving renal parenchyma. It is not a choice of drug in acute urinary tract infections. Sulfonamides should not be administered with methenamine because they form an insoluble complex with formaldehyde in urine resulting in antagonism. The drug is also used to control scour in pigs.

Dosage: Dog & Cat: 0.1-2.0 gm, orally, in 2-4 divided doses daily; Sow: 2-8 g, orally, twice daily; Horse: 8-15 gm, twice daily.

## EXERCISE

1. Give the source, antibacterial spectrum, mechanism of action and clinical uses of benzylpenicillin.
2. Give the classification of penicillins. Describe repository penicillins and potentiated penicillins.
3. What are semisynthetic penicillins? Describe their antibacterial spectrum and clinical application.
4. Classify the cephalosporins with suitable examples. Give their antibacterial spectrum and clinical uses.
5. Classify the aminocyclitol antibiotics based on their antibacterial spectrum. Discuss their common properties and mechanism of action.
6. Enlist the aminoglycoside antibiotics along with their source. Discuss their adverse reactions and clinical application.
7. Classify the tetracyclines. Describe their mechanism of action, antimicrobial spectrum and clinical application.
8. Name the semisynthetic tetracyclines. Describe pharmacokinetics, clinical application and adverse reactions of tetracyclines.
9. Describe the antibacterial spectrum, mechanism of action, pharmacokinetics and therapeutic application of chloramphenicol.
10. Name the macrolide antibiotics. Describe the antibacterial spectrum, mechanism of action and clinical application of eryhthromycin
11. What are fluoroquinolones? Describe their mechanism of action, antibacterial spectrum, pharmacokinetics and clinical uses.
12. **Write a short note on the following**:
    a) Semisynthetic penicillins
    b) Extended spectrum penicillins
    c) Repository penicillins
    d) Poteniated penicillins
    e) Toxicity of aminoglycoside antibiotics
    f) Properties of aminocyclitol antibiotics
    g) Lincosamide antibiotics
    h) Bacterial antibiotics
    i) Methenamine
    j) Polypeptide antibiotics
    k) Fluoroquinolones
    l) Polymyxins
    m) Cephamycins
    n) Erythromycin
    o) Chloramphenicol
    p) Rifamycins
    q) Cephalosporins

13. **What do you mean by the following? Answer in one or two sentences for each:**
    a) Beta-lactamases
    b) Penicillinase
    c) Cephalosporinase
    d) Penicillin unit
    e) Suicidal inhibition
14. **Differentiate between the following:**
    a) 6-aminopenicillanic acid and 7-aminocephalosporanic acid
    b) Benzylpenicillin and Benzathine penicillin G
    c) Penicillin G and Penicillin V
    d) Penicillin G and Oxacillin/Cloxacillin
    e) Repository penicillins and potentiated penicillins
    f) Repository and Semisynthetic penicillins
    g) Gentamicin and streptomycin
    h) Oxytetracycline and doxycycline/minocycline
    i) Chloramphenicol and florfenicol
    j) Quinolones and fluoroquinolones
    k) Nalidixic acid and ciprofloxacin
15. **Describe the mechanism of action of the following drugs:**
    a) Penicillins
    b) Cephalosporins
    c) Streptomycin
    d) Tetracyclines
    e) Chloramphenicol
    f) Erythromycin
    g) Fluoroquinolones
    h) Rifamycins
16. **Give the source of the following:**
    a) Penicillin
    b) Clavulanic acid
    c) Original cephalosporin
    d) Streptomycin
    e) Neomycin
    f) Kanamycin
    g) Gentamicin
    h) Tobramycin
    i) Sisomicin
    j) Chlortetracycline
    k) Oxytetracycline
    l) Demeclocycline
    m) Chloramphenicol
    n) Erythromycin
    o) Oleandomycin
    p) Spiramycin
    q) Tylosin
    r) Lincomycin
    s) Polymyxin B
    t) Colistin
    u) Bacitracin
    v) Vancomycin
    w) Tyrothricin
    x) Virginiamycin
    y) Tiamulin
    z) Novobiocin
    aa) Rifamycins
    bb) Cephalosporins
17. **Matching** (Parallel pairs)/**Multiple choices** (Right choices):
    a) Natural penicillin: Benzylpenicillin
    b) Soluble penicillin: Na/K salt of benzylpenicillin
    c) Sparingly soluble penicillins: Repository penicillins
    d) Repository penicillin: Proacaine penicillin G/Benzathine penicillin G
    e) Phenoxymethyl penicillin: Penicillin V
    f) Phenoxyethylpenicillin: Phenethecillin
    g) Acid resistant penicillin: Penicillin V/Ampicillin/Phenethecillin/Cloxacillin/Oxacillin/Flucoxacin/ Amoxicillin
    h) Acid labile penicillin: Methicilin/Nafcillin
    i) Penicillinase resistant penicillin: Methicillin/Nafcillin/Cloxacillin/Dicloxacillin/Flucoxacillin
    j) Extended spectrum penicillin:Aminopenicillins/Carboxypenicillins/Ureidopenicillins/Amdinopenicillins
    k) Aminopenicillin: Ampicillin/Bacampicillin/Talampicillin/Pivampicillin/Amoxicillin
    l) Bactericidal concentration of penicillins: 0.5 u/ml
    m) Carboxypenicillin: Carbenicillin/Ticarcillin
    n) Ureidopenicillin: Mezlocillin/Piperacillin
    o) Amidinopenicillin:Mecillinam/ Pivamecillnam
    p) Penicillin: Transpeptidase inhibition/Peptidoglycan synthesis/NAG-NAMA cross linking inhibition
    q) Orally ineffective/Acid labile penicillin: Penicillin G/Methicillin/Nafcillin
    r) Orally effective/Acid resistant penicillin: Ampicillin/Penicillin V/Cloxacillin/Oxacillin/Amoxicillin/ Phenethicillin/Flucoxacillin
    s) Penicillinase resistant penicillin: Methicillin/Nafcillin/Cloxacillin/Dicloxacillin/Flucoxacillin
    t) Extended spectrum penicillins: Aminopenicillins/Carboxypenicillins/Ureidopenicllins/Amidinopenicillins
    u) Beta-lactamase: Penicillinase/Cephalosporinase
    v) Beta-lactamase inhibitor: Clavulanic acid/Sulbactam/Tazobactam
    w) Nephrotoxic cephalosporin: Cephaloridine/Cephalothin
    x) Cephamycin: Cefmetazole/Cefotetan
    y) Dosage of bebzathine penicillin G/Penicillin V/Sodium penicillin G/Procaine penicillin G: IU/kg
    z) Dosage of semisynthetic penicillins: mg/kg
    aa) Synthetic cephamycin: Moxalactam
    bb) Monobactam: Aztreonam
    a) Carbapenem: Imipenem
    b) Cilastin: Inhibitor of dehydropeptidase I
    c) Imipenem: Hydrolyzed by renal tubular dehydropeptidase I
    d) Amikacin: Semisynthetic derivative of kanamycin

e) *Micromonospora* spp: Gentamicin/Sisomicin
f) Netilmicin: Semisynthetic derivative of sisomicin
g) Streptomycin: *Streptomyces griseus*
h) Neomycin: *Streptomyces fradiae*
i) Gentamicin: *Micromonospora purpurea*
j) Framycetin: *Streptomyces lavendulae*
k) Narrow spectrum aminoglycoside: Streptomycin
l) Extended spectrum aminoglycoside: Neomycin/Kanamycin
m) Broad spectrum aminoglycoside: Gentamicin/Amikacin/Sisomicin/Netilmicin
n) Spectinomycin: *Streptomyces spectabilis*
o) Chlotetracycline: *Streptomyces aureofaciens*
p) Oxytetracycline: *Streptomyces rimosus*
q) Chloramphenicol: *Streptomyces venezuelae*
r) Erythromycin: *Streptomyces erythreus*
s) Oleandomycin: *Streptomyces antibioticus*
t) Spiramycin: *Streptomyces ambofaciens*
u) Tylosin: *Streptomyces fradiae*
v) Bacitracin: *Bacillus subtilis*
w) Vancomycin: *Streptomyces orientalis*
x) Natural tetracycline: Chlortetracycline/Oxytetracycline/Demeclocycline
y) Semisynthetic tetracycline: Tetracycline/Methacycline/Rolitetracycline/Doxycycline/Minocycline
z) Short acting tetracycline: Tetracycline/Oxytetraccline/Chlortetracycline
a) Long acting tetracycline: Doxycycline/Minocycline
b) Intermediate acting tetracycline: Demeclocycline/Methacycline
c) Tetracycline entering CSF: Doxycycline/Minocycline
d) First synthetic antibiotic: Chloramphenicol
a) Chloramphenicol congeners: Thiamphenicol/Florfenicol/Less toxic to bone marrow
b) Grey baby syndrome: Chloramphenicol
c) Amidinopenicillin: Mecillinam/Pivecillin
d. Macrolide antibiotic: Erhthromycin/Oleandomycin/Spiramycin/Tylosin/Tilmicosin/Josamycin
e. Natural macrolide: Erythromycin/Oleandomycin
f. Semisynthetic macrolide: Azithromycin/Roxithromycin/Clarithromycin
g. Skeletal muscle relaxation: Aminoglycosides/Lincosamides/Polymyxins
h. Prodrug fluoroquinolone: Enrofloxacin
i. Fluoroquinolone crosses BBB: Pefloxacin
j. Polymyxins: Polypeptide Antibiotics/Nephrotoxicity/Neurotoxicity/Neuromuscular blockade
k. Bacterial antibiotic: Polymyxin B/Colistin/Bacitracin/Tyrothricin
l. Bacterial cell wall peptidoglycon: Penicillin/Bacitracin/Vancomycin/Cycloserine/Cephalosporins
m. Antidysenteric feed additive in piglets: Virginiamycin
n. Novobiocin: *Streptomyces niveus* and *S. spheroides*
o. Rifamycins: *Streptomyces mediterranei*
p. Polymyxin B: *Bacillus polymyxa*
q. Polymyxin E: *Bacillus colistinus*
r. Tyrothricin: *Bacillus brevis*
s. Tiamulin: *Pleurotus mutilis*
t. Rifampin/Rifamycin: AntiTB antibiotic
u. Rifampin: AntiTB drug/Enzyme inducer/Immunosuppression/Red-orange colored urine
v. Methenamine: Urinary antiseptic/Formaldehyde/Scour in pigs/Hexamine
w. One mg of penicillin G: 1667 units
x. One microgram of penicillin: 1.667 units
y. Fluoroquinolone orally used in vety. practice: Enrofloxacin
z. Cefoperazone/Ceftriaxone/Moxalactam: Antithrombin action/Hypothrombinemia/Bleeding syndrome
aa. Estimate to measure antibiotic concentration: MIC/MBC/MAC
bb. One unit of penicillin: 0.6 microgram of sodium penicillin

18. **Give the dose, route and frequency of administration of the following:**
a) Pencillin G in cattle
b) Procaine Penicillin G in a horse
c) Ampicillin in a dog
d) Cephalexin in a dog
e) Cefotaxime in a bitch
f) Ceftiofur in a cow
g) Cephalonium in a mastitic cow
h) Gentamicin in all animals
i) Amikacin in dog
j) OTC in systemic bacterial infection
k) Rolitetracycline/Florfenicol in cattle
l) Erythromycin in dog/cattle
m) Ciprofloxacin/Enrofloxacin in dogs.
n) Enrofloxacin in cattle

o) Streptomycin in *E. coli* mastitis in a cow

19. **What antibiotic you recommend for treatment of the following? Give its dose and route of administration:**
    a) Gram negative septicemia in bovines
    b) Tetanus in a kid/foal
    c) HS in a buffalo calf
    d) Anthrax in a heifer
    e) Brucellosis in a cow
    f) Treponema hyodysentery in a sow
    g) BQ in a calf
    h) Acute/Chronic urinary tract infection in a dog
    i) CRD in poultry
    j) Diarrhoea in calves
    k) Osteomyelitis in a dog/cat
    l) Meningitis in dog/cat
    m) Actinomycosis in a cow
    n) Colibacillosis/Pneumonia in calves
    o) CBPP in a buffalo.
    p) Rickettsial infection in a dog/cat
    q) TB in a dod/cat
    r) Bronchopneumonia in cattle
    s) Metritis in ewe/sow
    t) Secondary bacterial infection in FMD/Canine distemper
    u) Anaerobic Gram negative septicemia in cattle
    v) Brain abscess in a dog
    w) Oitis externa in a cat/dog
    x) Leptospirosis in cattle
    y) Bone infection in a dog
    z) Upper respiratory tract infection in a dog
    aa) Gram positive pneumonia in a dog allergic to penicillin

20. **Substantiate each of the following by giving the most appropriate reason:**
    a) Penicillin G has narrow antimicrobial spectrum.
    b) Penicillin discovery was accidental.
    c) Na/K benzylpenicillin is ineffective orally.
    d) Na/K benzylpenicillin is short acting.
    e) Procaine penicillin G/Benzathine penicillin G exerts long duration of action.
    f) Ampicillin/Penicillin V/Cloxacillin/Amoxicillin/Oxacillin can be given orally.
    g) Probenecid prolongs antibacterial action of penicillins.
    h) Repository penicillins should not be injected IV.
    i) Probenecid extends the plasma half-life of penicillins.
    j) Beta-lactamase producing bacteria are insensitive to penicillins/cephalosporins.
    k) Clavulanic acid/Sulbactam/Tazobactam potentiates penicillins
    l) Augmentin/Timentin is a potentiated penicillin.
    m) Clavulanic acid-amoxicillin/Clavulonic acid-ticarcillin/Sulbactam-ampicillin is a potentiated penicillin.
    n) Bacteria develop cross resistance to penicillins and cephalosporins.
    o) Imipenem is used in combination with cilastin.
    p) Aminoglycoside antibiotics are bactericidal.
    q) Netilmicin is effective against gentamicin resistant bacterial strains.
    r) Aminoglycoside antibiotics cause ototoxicity.
    s) Aminoglycoside antibiotics cause deafness.
    t) Aminoglycoside antibiotics cause vertigo/ataxia.
    u) Netilmicin is preferred for long term use.
    v) Aminoglycoside antibiotics cause neuromuscular blockade/skeletal muscle paralysis.
    w) d-Tubocurarine must be used in caution in animals treated with aminoglycoside antibiotics.
    x) Inhalation anaesthetics should be used with caution in aminoglycoside antibiotic-treated animals.
    y) Tetracyclines differ from penicillin G or streptomycin.
    a) Tetracyclines have wide spectrum of antimicrobial action.
    b) Doxycycline/Minocycline exerts long duration antibacterial activity.
    c) Orally administered tetracyclines are ineffective in animal pre-treated with milk and milk products, salts of Ca, Mg or Fe and antacids.
    d) GI absorption of doxycycline and minocycline is complete in animals which ingested milk and milk products, salts of Ca, Mg or Fe and antacids.
    e) Tetracyclines get deposited in growing bones or teeth.

f) Doxycycline and minocycline can be used in meningitis.
g) Tetracyclines have broad antimicrobial spectrum of activity.
h) Oral dosing of tetracyclines may lead to B-complex and vitamin K deficiency.
i) Tetracyclines cause bone and teeth abnormalities.
j) Intramammary infusion of chlortetracycline in mastitic dry cows is contraindicated.
k) Tetracyclines should never be mixed with penicillins.
l) Doxycline/Minocycline is a long acting tetracycline.
m) Chloramphenicol is of historical significance.
n) Chloramphenicol is ineffective orally in ruminants.
o) Chloramphenicol and vaccination should be avoided.
p) Macrolides should not be administered with chloramphenicol.
q) Spiramycin is the preferred macrolide antibiotic in treating contagious bovine pleuropneumonia.
r) Fluoroquinolones are the preferred antibiotics for blind therapy in infectious diseases.
s) Tiamulin and ionophores should not be concurrently included as feed additives in poultry.
t) Sulfonamides should not be administered to methenamine-treated animals.
u) Chloramphenicol potentiates action of local anaesthetics.
v) Polymyxin B is added to bull semen.
w) Neomycin is contraindicated in animals with post-parturient hypocalcemia.
x) Aminoglycoside antibiotics should be avoided in pregnant animals.
y) Chloramphenicol antagonizes the action of macrolide antibiotics and clindamycin.
z) Neostigmine reverses neuromuscular blockade of aminoglycoside antibiotics.
a) Fluoroquinolones should not be used in pups.
b) Vitamin K prophylaxis is suggested before use of moxalactam.
c) Some cephalosporins (Cefoperazine/ceftriaxone/moxalactam) promote bleeding.
d) Demeclocycline causes diuresis.
e) Clavulanic acid/Sulbactam/Trazobactam antagonizes the action of penicillin

# Chapter – 35: ANTIFUNGAL AGENTS

These are the drugs which kill or inhibit the growth of fungus in the body of the host and are used for superficial and deep (systemic) mycoses. Some fungal infections are self-limiting (get cured without treatment).

Clinically fungal infections in animals can be classified into two groups:

1. Superficial fungal infections: Include dermatophytoses of the skin, hair and nails (caused by *Trichophyton*, *Microsporum* or *Epidermophyton* spp) and candidiasis or moniliasis of the moist skin and mucous membrane (GIT and genital tract).
2. Systemic (Deep) mycoses: Systemic fungal infections (Coccidioidiomycosis, histoplasmosis, cryptococcsis, candidiasis or blastomycosis etc).

Antifungal agents can be classified in two groups based on their mode application:

A. **Systemic Agents**: These are used in the treatment of fungal infections of internal organs or GIT. Some of these may also be useful in treating dermatomycoses (via blood and enter keratin producing cells in the skin).

B. **Topical Agents**: These are used for treating superficial fungal infections, usually applied topically. Griseovulvin is used to treat dermatomycoses, but administered orally (after absorption enters in the keratin producing cells in the skin via the circulation). A topical agent used for dermatophytoses should have both fungistatic and keratolytic properties; otherwise it should be combined with a keratolytic agent so that it can remove the keratin layer and facilitate the surface contact of the drug and the fungus.

## 1. Systemic Antifungal Agents

**1. Polyene Antifungal Antibiotics**: Amphotericin B, Nystatin, Natamycin (Pimaricin).

**Amphotericin B**: It is obtained from a strain of *Streptomyces nodosus*. It is active against a wide range of fungi. It remains the principal drug to be used against deep seated systemic mycotic infections despite its toxicities. It is administered as IV infusion in the form of colloidal suspension. The drug is not absorbed orally and therefore it is only given by this route for fungal infections of the GI tract (intestinal candidiasis). Its penetration into CSF is poor. The drug is used in the treatment of histoplasmosis, blastomycosis, coccidioidiomycosis, cryptococcosis and candidiasis. It is also used topically to treat mucocutaneous candidiasis. Monitoring of BUN/creatinine is necessary in animals undergoing amphotericin B therapy (renal toxicity).

Mechanism of Action.

Polyenes have high affinity for the ergosterol component present in the fungal cell membrane. They bind with ergosterol and form pores in the membrane and thereby interfere with the fungal cell membrane permeability and transport functions. There is efflux of intracellular $K^+$ from fungal cells and influx of $H^+$, causing internal acidification of fungal cell and halt in enzymatic processes. The sugars, amino acids and other water soluble substances also leak out of the cell. These mechanisms result in fungicidal action. In addition, amphotericin B also acts as an immunostimulant in animals.

Bacteria do not have sterols in their cell membrane and are insensitive to polyenes. Cholesterol, present in mammalian cell membrane, resembles to ergosterol and polyenes bind to it as well, though with lesser affinity. Therefore, selectivity of polyenes is low and amphotericin B is one of the most toxic (neprotoxic and anaphylactic) systemically used antifungal antibiotic, but it is the least toxic among polyenes. Amphotericin B increases the antifungal action of flucytosine and their combination is the drug of choice in cryptococcal infection (meningitis).

Dose: Amphotericin B (0.1 mg/ml in 5% dextrose): @ 0.1-1 mg/kg, slowIV, 3 times per week (total dose: 4-11 mg /kg).

**Nystatin**: Antifungal antibiotic obtained from *Streptomyces noursei*. Its antifungal action and other properties are similar to Amphotericin B; but because of higher systemic toxicity its usefulness is limited to

treatment of *Candida* infections of the skin, mucous membrane and GI tract and applied either orally or topically. Its oral absorption is poor. It is the drug of choice for prevention and treatment of intestinal moniliasis.
Dose: Oral: @ 22,000 iu/kg/day in three divided doses.

**Natamycin (Pimaricin)**: It is similar to nystatin and primarily used in the treatment of fungal keratitis. A 5% ophthalmic solution applied topically 1 drop instilled in the eye every 1-2 hr.

**2. Azoles:** The clinically important members are:
**a. Imidazoles:** Topical: Clotrimazole, Econazole and Miconazole; Systemic: Ketoconazole and Thiabendazole
**b. Triazoles**: Systemic: Fluconazole and Itraconazole.
Imidazoles and triazoles have broad spectrum fungistatic activity, covering dermatophytes, *Candida* and some are also effective against systemic mycoses.
They inhibit fungal cytochrome P450 enzyme, lanosine 14-alpha-demethylase which coverts lanosterol to ergosterol (the main sterol in the fungal cell membrane).The interference in ergosterol synthesis leads to structural and functional (enzymatic) abnormalities in the fungal cell membrane. Triazoles are less toxic than imidazoles because of their lower affinity for mammalian Cytochrome P450 and cause less interference with mammalian sterol synthesis.

**Ketoconazole**: It is the first orally effective broad spectrum antifungal drug, useful in both dermatophytosis and deep/systemic mycoses. Administered orally, it is effective in the treatment dermatophytosis (alternative to griseofulvin) and also very effective in histoplasmosis, blastomycosis, coccidioidiomycosis, cryptococcsis and mucocutaneous candidiasis. It is less potent, but much less toxic than Amphotericin B. Orally it is well absorbed and absorption is facilitated by gastric acidity (more soluble at lower pH). Azoles are widely distributed in the body, their CSF penetration is poor (largely bound to albumin), except fluconazole, undergo extensive hepatic metabolism and excreted in urine and faeces. Ketoconazole causes microsomal enzyme inhibition and thus inhibits the metabolism of many drugs, also inhibits steroidogenesis. It can be used along with Amphotericin B or 5-Flucytosine to potentiate its antifungal activity. It causes GI disturbances, hormonal and reproductive disorder in dogs. It should not be given to pregnant animals (teratogenic).
Dose: Dogs: @ 5-20 mg/kg, twice daily.

**Fluconazole and Itraconazole**: Their pharmacological properties are similar to ketoconazole, but have wider range of antifungal activity and are less toxic; hence preferred for the treatment of systemic mycoses. Fluconazole has high tissue (including CSF) penetrability and low nephrotoxicity (combined with Amphotericin B in treating cryptococcal meningitis).
Dose: Fluconazole and Itraconazole: @ Dogs: @ 5-10 mg/kg, twice daily.

**Flucytosine**: It is a synthetic narrow spectrum fungistatic drug, active against few strains of *Cryptococcus, Candida, Aspergillus* and *Chromoblastomyces* spp. The other fungi causing systemic mycoses, dermatomycoses and bacteria are insensitive to flucytosine. It is a pyrimidine antimetabolite and inactive as such. It is converted to the antimetabolite, 5-fluorouracil (5-FU) by cytosine deaminase in the fungal but not in mammalian cells. 5-FU inhibits thymidylate synthetase and thus DNA synthesis. Mammalian cells are not affected because of very limited ability to convert flucytosine to 5-FU. It is rapidly absorbed orally, widely distributed in the body and has excellent penetration to tissues and fluids including CSF. Its main indications are cryptococcal meningitis (in combination with Amphotericin B), candidiasis, aspergillosis and chromomycosis. It is less toxic than Amphotericin B.
Dose: Oral: Dogs: 25-50 mg/kg, thrice a day; Cats: 30-40 mg/kg thrice a day.

## 2. Topical Antifungal Agents

**Griseofulvin**: It is obtained from a fungus *Penicillium griseofulvum*. It is a narrow spectrum fungistatic agent, active against most dermatophytes and administered orally for treatment of ringworm in dogs, cats, calves, horses and other domestic animals, along with a topical antifungal agent. It is ineffective against *Candida* and other fungi causing systemic mycoses and bacteria. High dietary fat intake promotes absorption of griseofulvin from GIT. Dermatophytes selectively concentrate griseofulvin by an active process. It first interacts with polymerized microtubules thus causing disruption of mitotic spindle in susceptible dermatophytes and this result in interference with mitosis. After oral administration the absorbed drug gets deposited in the keratin precursor cells of stratum corneum, exerts fungistaic action and prevents fungal invasion of deeper layers. The superficial cells containing the fungus and keratin are shed off and replaced by healthy cells from the deeper layer of the skin. The treatment should be continued at least one week after the disappearance of clinical signs. It is the drug of choice in treatment and prevention of ringworm in calves.
Oral Dose: Dog & cat: @ 10-30 mg/kg/day in one or two divided doses for 4-8 weeks; Horse and cattle: @ 5-10 mg/kg/day in one or two divided doses for 4-8 weeks.

A large number of antifungal agents are also applied topically, on the skin, in the ear or eye or on the mucous membrane to control superficial/local fungal infections. The drugs are:
**Undecylenic acid (10% powder or alcoholic solution)**: Has potent fungistatic activity and used in superficial fungal infections and to treat fungal mastitis. Other fatty acids like caprylic acid and propionic acid also have fungistatic action.

**Salicylic acid**: It has fungistatic action and is a component of many topical antifungal preparations because of its good keratolytic activity. It is mainly used to treat chronic superficial dermatomycoses.

**Benzoic acid**: Both salicylic acid (3%) and benzoic acid (6%) are used to prepare Whitfield ointment, an antifungal ointment. Benzoic acid has both fungistatic as well as keratolytic activity. It is used in dermatomycoses.

**Tolnaftate (1% lotion)**: It is active against dermatophytes, but not against *Candida* and bacteria. It is used topically with oral griseofulvin.

**Ciclopirox olamine (1% lotion)**: It is a broad spectrum antifungal drug, active against all dermatophytes and *Candida*. It is used to treat dermatomycoses and *Candida* infections.

**Haloprogin (1% cream)**: A synthetic antifungal agent used to treat dermatomycoses in dogs.

**Candidicin**: A fungistatic and fungicidal antibiotic, active against *Candida* and mainly used in moniliasis also used in dermatomycoses (ringworm).

**Iodochlorhydroxyquin (3% cream/ointment/powder)**: Possess both antibacterial and antifungal activity and used topically to treat mixed infections.

**Cuprimyxin**: It has antifungal as well as broad spectrum antibacterial activity (active myxin is released on application) and used topically.

**Imidazoles**: These include **Clotrmazole** (1% cream or lotion) and **miconazole** (2% cream or lotion) are used topically against dermatophytes and candidiasis. **Econazole** (1% cream) most active topical imidazole, used especially in candidiasis. **Thiabendazole** is given topically or orally in calves to treat ringworm infection (@ 22 mg/kg, twice a day orally).

**Amorolfine**: It is topically used to treat dermatophytoses.

**Terbinafine**: It is occasionally used in dogs and cats topically (as 1% cream) or orally (@5 mg/kg/day for 7 weeks) against dermatophytes and *Candida*. It decreases ergosterol synthesis in fungus.

**Other agents**: **Phenols, iodine and mercurials** have antibacterial as well as antifungal activity; but they may cause normal tissue damage. **Carbol-fuchsin** solution is also applied topically, twice daily for 7 days. **Gentian violet** is used in candidiasis. Topical antifungal preparations generally contain an antipruritic, a corticisteroid and an antihistamine in addition to the antifungal agent.

EXERCISE

1. Classify the antifungal agents and discuss the pharmacology of polyene antifungal antibiotics.
2. What are systemic antifungal agents? Discuss the pharmacology of azole antifungal agents.

3. **Write a short note on the following**:
   a) Topical antifungal agents
   b) Polyene antifungal antibiotics
   c) Triazole antifungal agents
   d) Imidazole antifungal agents

4. **Describe mechanism of action of the following**:
   a) Amphotericin B
   b) Nystatin
   c) Griseofulvin
   d) Ketoconazole
   e) Flucytosine
   f) Polyene antifungal agents
   g) Azole antifungal agents

5. **Differentiate between the following**:
   a) Systemic and topical antifungal agents
   b) Amphotericin B and Ketoconazole
   c) Flucytosine and Amphotericin B
   d) Imidazole and triazole antifungal agents
   e) Ketoconazole and fluconazole
   f) Salicylic acid and benzoic acid
   g) Griseofulvin and Amphotericin B

6. **Matching** (Parallel pairs)/**Multiple choices** (Correct choices):
   a) Antifungal antibiotic: Amphotericin B/ Nystatin/Natamycin/Griseofulvin
   b) Imidazole antifungal agent: Clotrimazole/Econazole/Miconazole/Ketoconazole/Thiabendazole
   c) Triazole antifungal agent: Fluconazole/Itraconazole
   d) Dermatophytoses: Clotrimazole/Econazole/Miconazole/Griseofulvin/Undecylenic acid//Benzoic acid Tolnaftate/ salicylic acid/Ciclopirx/Haloprogin/Candidicin/Iodochlorohydroxyquin/Cuprimyxin/ Clotrimazole/Miconazole/Thiabebdazole/Terbinafine/Phenols/Iodine/Mercurials/Gentian violet
   e) Systemic mycoses: Amphotericin B/Nystatin/Ketoconazole/Fluconazole/Itraconazole/Flucytosine
   f) Dermatophytoses and systemic mycoses: Imidazoles/Ketoconazole/Flucytosine
   g) Fungicidal: Amphotericin B/Nystatin/Natamycin
   h) Fungistatic: Griseofulvin/Imidazoles/Triazoles/Ketoconazle/Fluconazole/Itraconazole/Flucytosine
   i) Amphotericin B: *Streptomyces nodosus*
   j) Nystatin: *Streptomyces nouresi*
   k) Iodochlorhydroxyquin: Antibacterial/Antifungal/Mixed infections
   l) Thiabendazole: Anthelmintic/Antifungal
   m) Whitfield ointment: Salicylic acid/Benzoic acid/Salicylic acid and Benzoic acid/Fungistatic/keratolytic
   n) Fungistatic: Undecylenic acid/Caprylic acid/Propionic acid
   o) Topical antifungal agent: Fungistatic/Fungicidal/Keratolytic
   p) Imidazoles: Antibacterial/Anthelmintic/Antiprotozoal/Antifungal
   q) Topical antifungal formulation: Antifungal agent/Antipruritic/Antihistamine/Glucocorticoid
   r) Griseofulvin: *Penicillium griseofulvun*
   s) Candidicin: Topical antifungal antibiotic
   t) Fungal mastitis: Undecylenic acid
   u) Pulmonary aspergillosis: Nystatin
   v) Amphotericin B: Histoplasmosis/Aspergillosis
   w) Miconazole: Systemic fungal infection
   x) Blastomycosis: Itraconazole
   y) Coccidiomycosis: Fluconazole
   z) Flucytocine: Cryptococcal & systemic candidiasis
   aa) Thiabendazole: Reduce aflatoxin production in feed

bb) Haloprogin: Synthetic antifungal agent irritant to eye
cc) Systemic candidiasis: Amphotericin B/Flucytocine/Fluconazole
dd) Cryptococcal meningitis: Amphotericin B/Flucytosine/Fluconazole/Itraconazole
ee) Systemic aspergillosis/Blastomycosis: Itraconazole/Amphotericin B
ff) Histoplasmisis: Amphotericin B/Itraconazole/Fluconazole
gg) Coccidiomycosis: Flucanazole/Itraconazole/Amphotericin B
hh) Fluconazole Drug of choice: Systemic candidiasis/Cryptococcal meningitis
ii) Amphotericin B Drug of choice: Systemic aspergillosis/Blastomycosis

7. **Give most appropriate reason for each of the following statements:**
   a) An ideal antifungal agent for dermatophytoses should also possess keratolytic activity.
   b) Whitfield ointment is an ideal topical antifungal agent.
   c) Polyene antifungal antibiotics/Amphotericin B exert (s) fungicidal action.
   d) Bacteria are insensitive to polyene antibiotics.
   e) Griseofulvin though it is ineffective against systemic mycoses it is administered systemically.
   f) Griseofulvin exerts fungistatic action.
   g) Ketoconazole inhibits metabolism of several other drugs
   h) The antifungal action of flucytosine involves formation of antimetabolite.
   i) Flucytosine does not exert antimetabolite action on mammalian cells.
   j) Salicylic acid is a common component of many topical antifungal preparations.
   k) Some fungal infections are self-limiting.
   l) Fat-rich diet is recommended in animals under griseofulvin treatment.
   m) Ketoconazole may induce signs of hypoadrenocortical signs.

8. **Give the dose, route and frequency of administration of the following:**
   a) Griseofulvin in a horse/dog
   b) Amphotericin B in animals
   c) Ketoconazole in a dog/cat
   d) Fluconazole in a cat/dog

9. **Give the drug of choice for treatment of the following. Mention its dose and route of administration:**
   a) Dermatophytosis in a horse/dog
   b) Cryptococcal meningitis in a dog
   c) Histoplasmosis in a calf
   d) Intestinal candidiasis in a foal

# Chapter – 36: ANTIVIRAL DRUGS

**Principles of Antiviral Chemotherapy:** Viruses are obligate intracellular parasites which cannot replicate independently and must utilize the host's cell pathways of energy generation, protein synthesis, DNA and RNA replication for their multiplication. Drugs that affect the viral processes must penetrate the host cells and in doing so, they are likely to adversely affect the normal pathways of host cell. Because of this close association between virus and host cell, chemotherapy of viral diseases is difficult and antiviral drugs are generally having narrow margin of safety. However, virus directed enzymes have been characterized in infected cells and these may have higher affinity for some inhibitors or antimetabolites than the normal host cell enzymes.

Most of the antiviral drugs are nucleic acid analogs and interfere with the viral nucleic acid synthesis (DNA or RNA) or regulation. Drugs may also affect virus specific steps like attachment to host cell, penetration and uncoating of virus in host cell, reverse transcription, virus assembly and maturation.

The general approach to the control of viral diseases is to develop effective vaccines, but this may not be always possible and in such cases chemotherapy is the only alternative. The main objective of antiviral chemotherapy is to eradicate the virus with little or no damage to the host and to prevent further viral infection. Only a few antiviral drugs have so far been developed which are somewhat safe and effective against limited viral diseases. Most of these drugs have been developed for human use and only a few have been studied in animals. In most of the acute viral diseases, the replication of viruses reaches peak when symptoms appear. Most antiviral drugs have greater effect against fewer infectious particles and show less efficacy when the disease is symptomatic. Therefore, antiviral drugs should be started early in the incubation period or such drugs may be useful as a chemoprophylactic agents.

**Classification of Antiviral Drugs:**

**A. Based on Mechanism of Action:**

1. Preventing viral attachment to and penetration of host cells: Amantadine and rimantadine.
2. Neuraminidase inhibitors: Oseltamivir (tamiflu) and zanamivir
3. Transcription analogs: Idoxuridine, ribavirin and trifluorothymidine (trifluridine)
4. Late translation inhibitors: Methisazone and interferons
5. DNA polymerase and DNA synthesis inhibitors: Acyclovir, famciclovir, ganciclovir, cytarabine, vidarabine and foscarnet
6. Reverse transcriptase inhibitors: Zidovudine, didanosine and stavudine
7. Protease inhibitors: Sanquinavir, indinavir, ritonavir and nelfinavir
8. Interference in protein synthesis: Mitomycin and puromycin
9. Interference with viral maturation: Rifamycin and streptovaricin
10. Host immunomodulators: Interferons, Gamma-globulin, poly I. Poly C, BRL-5907 and levamisole

**A. Based on Type of Virus Affected:**

1. Antiherpes virus: Idoxuridine, trifluridine, vidarabine, cytarabine, acyclovir, ganciclovir, panciclovir, cidofovir, foscarnet etc.
2. Antiretrovirus: Zidovudine, stavudine, didanosine; Sanquinavir, indinavir, ritonavir and nelfinavir
3. Antiinfluenza virus: Amantadine, rimantadine, oseltamivir and zanamivir
4. Antipox virus: Methisazone
5. Antiviral antibiotics: Rifampin, bleomycin, actinomycin D, mitomycin and puromycin
6. Nonselective: Interferon, interferon inducers (Poly-I. Poly-C and BRL-5907), γ-globulins and levamisole.

**Idoxuridine**: First antiviral drug used clinically (in man). It is a pyrimidine nucleoside. Being a thymidine analog, it competes with thymidine and gets incorporated in DNA resulting in formation of faulty DNA which breaks down easily. This DNA directs the synthesis of wrong viral proteins. Viral components are produced in the host cells but infective viruses do not arise. It is effective against DNA viruses only and is indicated in the treatment of corneal and skin infections with Herpes virus in man and animals. It has high systemic toxicity (bone marrow depression). Acyclovir is an equally effective and better tolerated alternative; It is used as 0.1% ophthalmic solution, 1 drop, topically, every 1-2 hr.

**Trifluridine**: It is related to idoxuridine and analog of deoxythymidine. It is the current drug of choice for *Herpes simplex* keratitis in man. It is used as 1% ophthalmic solution, 1 drop topically, every 2 hr for 2 days and then 4-8 times daily.

**Cytarabine (Cytosine arabinoside; Ara-C)**: It is an analog of cytosine deoxyribose. In cell culture, it has activity against herpes virus, pox virus, vaccinia and rabies virus. It has topical activity against herpes virus and vaccinia keratitis, but systemic antiviral activity has not been established.

**Vidarabine (Adenine arabinoside; Ara-A)**: It is an adenine analog which is phosphorylated by cellular enzymes to triphosphate that inhibits many viral and human DNA polymerases and thus the DNA synthesis. It is more selective than idoxuridine, but less so than acyclovir. It is used topically for ocular herpes infection and systemically for *Herpes simplex* encephalitis, for mucocutaneous herpes and pox virus infections, but now has been replaced by acyclovir. It may produce bone marrow and CNS toxicity at higher doses. It is applied as 3% ophthalmic ointment, 0.5 cm ointment, applied topically, every 5-6 hr, 3-6 times daily. In injection form (200mg/ml) @ 10-30 mg/kg IV once daily.

**Ribavirin (Tribavirin)**: A synthetic purine nucleoside and analog of guanosine. It has broad spectrum antiviral activity against many RNA and DNA viruses like adeno, herpes, orthomyxo, paramyxo, pox, picorna, rhabdo, rota and retro viruses. Its mono and triphosphate derivatives generated intracellularly inhibit GTP and viral RNA and polypeptide synthesis. It is administered topically, orally, IV or as aerosol in influenza, measles, herpes infection, acute hepatitis and viral bronchitis in human. It may cause GI disturbances, bone marrow depression and anaemia. It has low margin of safety in domesticated animals. Dose: 11 mg/kg, IV once daily for 7 days; Oral: 20 mg, four times daily.

**Acyclovir**: A deoxyguanosine analog, having an unique mode of action. It is initially phosphorylated to acyclovir-monophosphate by a virus specific thymidine kinase and this monophosphate is again phosphorylated to acyclovir triphosphate by cellular kinases. The acyclovir triphosphate competitively inhibits herpes virus DNA polymerase and also gets incorporated in viral DNA and stops lengthening of DNA strand. The terminated DNA inhibits DNA polymerase irreversibly and thereby stops DNA synthesis. Acyclovir is a relatively safe antiviral drug having wide margin of safety. It is widely used in *H. simplex* infection and in chicken pox (IV) in man and in feline *Herpes* virus infection (200 mg, orally four times daily). Its preparations and doses are
5% cutaneous ointment 6 times daily for 10 days.
Tablet (200 mg): Oral: @ 15 mg/kg/day for 7-10 days.
Injection (500 mg/vial powder): @ 5-10 mg/kg/day IV for 7-10 days.

**Ganciclovir**: A synthetic guanine analog, also an antiviral purine nucleoside, having virus specificity and mechanism of action similar to acyclovir. It has high systemic toxicity (bone marrow depression, neurological toxicity) and use is restricted in the prevention and treatment of cytomegalovirus (CMV; severe retinitis) infection in immunocompromised patient. Dose: @ 10 mg/kg/day IV.

**Foscarnet**: A phosphonate, acts by inhibiting viral DNA polymerase and reverse transcriptase. It has high nephrotoxicity. Its clinical use is similar to ganciclovir.

**Zidovudine (Azidothymidine; AZT)**: This is a thymidine analog, mainly effective against retroviruses and used in the treatment of human immuno deficiency virus (HIV; a double stranded DNA virus) infections. After phosphorylation in the body zidovudine triphosphate selectively inhibits viral reverse transcriptase (RNA dependent DNA polymerase; required to convert single stranded viral RNA to double stranded viral DNA) in preference to host cellular DNA polymerase. The current choice of drug in HIV treatment.
Dose: 500 mg/day, orally in 2-4 divided doses with plenty of water.

**Sanquinavir, indinavir, ritonavir and nelfinavir**: In HIV, the viral mRNA transcribed from the provirus is translated into two inert polyproteins. A virus specific protease converts these polyproteins into various structural and functional proteins by cleavage at specific positions. HIV specific protease inhibitors bind to the site where cleavage occurs and thereby inhibit the synthesis of viral proteins. Since the protease does not occur in the host, these drugs are highly effective in therapy of AIDS in combination with reverse transcriptase inhibitors.

**Didanosine and stavudine** are pharmacologically similar to zidovudine and they are indicated in HIV patient not tolerating AZT or for AZT resistant HIV.

**Methisazone**: An isatin-3-semicarbazone, effective against pox and adeno viruses. It is used in the treatment (less active) and prevention of small pox in man. It must be administered orally (less solublity); may cause anorexia and vomotion. It acts by preventing the replication of virus by inhibiting late translation of mRNA thereby blocking the synthesis of structural proteins.

**Amantadine**: A cyclic amine highly effective against influenza virus. It is not a virucide, but blocks the penetration of the virus into the host cell and inhibits the uncoating of the virus particle. It also interferes with the early stage of viral mRNA transcription. It is indicated in prevention and treatment of influenza A virus infection in man and influenza infection in chicken, turkeys and horses. It is well absorbed orally. It may cause CNS stimulation at high doses.
Dose: Man: Adult: 100 mg capsule orally, twice daily; Child: 5 mg/kg/day orally); Chickens: 25 mg/kg in drinking water.
**Rimantadine** is a more potent and long acting derivative. Dose: Man: 200 mg, orally once daily.
**Oseltamivir and zanamivir**: In influenza virus, the action of neuraminidase is involved in the budding of new virus from infected cells; these drugs act by inhibiting the action of this enzyme. In treatment of **bird flu** these drugs are commonly used. The bird flu virus may show resistance to amantadine or rimantadine; hence oseltamivir or zanamivir are preferred.

**Rifamycins (Rifampin)**: Inhibit viral mRNA polymerase and interfere with the assembly of viral proteins and maturation of virus.

**Interferons**: Interferons are a group of proteins liberated by mammalian cells infected by viruses. They make the neighbouring cells less susceptible to viral infection and contribute to the host's resistance.. They have nonspecific antiviral activity and inhibit many RNA and DNA viruses. However, they are more specifically effective against its specific inducer virus. They are host specific and interferon from one species cannot be used to protect another. Three types of interferons have been detected: alpha, beta and gamma. They are produced by recombinant DNA technology. Interferons bind with specific cell surface receptors and affect the replication of virus at various steps. The most important effect is inhibition of viral mRNA and protein synthesis. Besides this, they also affect the virus penetration, assembly of viral particles and their release.

**Interferon Inducers:** These protect animals against viral infection.
**Polyribioinosinic acid (Poly-I). polyribocytidylic acid (PolyC)** used in viral hepatitis in dogs and rabies in mice. **BRL 5907** (a metabolite of a fungus) contains double stranded RNA; protects cattle against FMD virus, if given before challenge.

**Gammaglobulins**: Are concentrated antibodies extracted from normal blood may also be useful in preventing viral infections (prophylaxis) in man and animals.

**Levamisole**: Primarily used as anthelmintic, but also has immunostimulant action. Herpes infection in man responds to levamisole.

**Antiviral drugs used in AIDS (HIV protease inhibitors)**: Saquinavir, ritonavir, indinavir, nelfinavir and amprenavir.

EXERCISE

1. Describe the different mechanisms through which drugs exert antiviral action, citing suitable example of antiviral drug for each.

2. **Write a short note on the following**:
   a) Thymidine analog antiviral drugs
   b) Guanosine analog antiviral drugs
   c) Clinical use of antiviral drugs in veterinary practice
   d) Mechanisms of antiviral actions
   e) Interferons
   f) Interferon inducers
   g) Treatment/Control of bird flu

3. **Describe mechanism of action of the following**:
   a) Idoxuridine
   b) Cytarabine
   c) Vidarabine
   d) Ribavirin
   e) Acyclovir
   f) Ganciclovir
   g) Foscarnet
   h) Zidovudine
   i) Amantadine
   j) Rimantadine
   k) Interferons
   l) Poly I. Poly C
   m) Oseltamivir/Tamiflu
   n) Methisazone
   o) Sanquinavir

4. **Matching** (Parallel pairs)/**Multiple choices** (Correct choices):
   a) Prevents virus entry into host cells: Amantadine/Rimantadine
   b) Faulty viral DNA formation: Idoxuridine/Trifluridine
   c) Inhibition of viral DNA polymerase: Vidarabine/Acyclovir/Ganciclovir/Foscarnet
   d) Effective against RNA and DNA viruses: Ribavirin/Interferons
   e) Inhibition of viral reverse transciptase: Zidovudine/Didanosine/Stavudine
   f) Interferons: Inhibition of viral mRNA synthesis/Inhibition of protein synthesis/Affect viral penetration
   g) Interferon inducer: Poly-I/Poly-C/ BRL-5907
   h) Rabies in mice: Poly-I.Poly-C
   i) Viral hepatitis in dog: Poly-I. Poly-C
   j) BRL-5907: Fungal metabolite/Interferon inducer/Protection against FMD
   k) Viral thymidine analogs: Idoxuridine/Trifluridine/Zidovudine
   l) Viral cytosine analog: Cytarabine
   m) Viral guanosine analog: Rabavirin/Acyclovir/Ganciclovir
   n) Antiviral phosphonate: Foscarnet
   o) Antiviral cyclic amine: Amantadanie
   p) Antiherpes virus: Idoxuridine/Trifluridine/Vidarabine/Cytarabine/Acyclovir/Ganciclovir/Foscarnet
   q) Antiretrovirus: Zidovudine/Stavudine/Didanosine
   r) Influenza virus: Amantadine/Rimantadine/Oseltamivir/Tamiflu/Zanamivir
   s) Antipox: Methisazone
   t) Antiviral antibiotics: Rifampin/Bleomycin/Actinomycin D/Mitomycin/Puromycin

u) Topical antiviral activity: Cytarabine
v) Broad spectrum antiviral: Ribavirn
w) Treatment of HIV: Zidovudine/Didanosine/Stavudine
x) Gammaglobulins: Viral antibodies
y) Idoxuridine: First clinically used antiviral drug/ Bone marrow depression
z) Neuraminidase inhibitor: Oseltamivir/Tamiflu/Zanamivir/Antiviral drug
aa) Viral protease inhibitor: Antiviral drug/Sanquinavir/Indinavir/Ritonavir/Nelfinavir

5. **Give most appropriate reason for each of the following statements**:
a) Levamisole, though not an antiviral drug, is beneficial in viral diseases.
b) Antiviral drugs exhibit narrow margin of safety.
c) Antiviral therapy must be instituted very early in the course of incubation period of a viral disease.
d) Antiviral drugs may be useful as chemoprophylactics of viral diseases.
e) Idoxuridine/Trifluridine exerts antiviral action through formation of faulty viral DNA.
f) Vidarabine inhibits viral DNA synthesis.
g) Acyclovir/Ganciclovir inhibits viral DNA synthesis.
h) Zidovudine has preferential action on viral cells as compared to host's cells.
i) Amantadine/Ramantadine is not a virucide, but exerts antiviral action.
j) Interferons cannot be used as antiviral agents universally.
k) The antiviral action of Poly I.PolyC/BRL 5907 is through interferons.

# Chapter – 37: ANTISEPTICS AND DISINFECTANTS

The chemicals used for the purpose of non-selective killing or inhibiting the growth of microbes (bacteria, viruses, fungi and protozoa etc) on contact are called as germicides. Their actions may range from reducing the number of microbes within safe limits (sanitation) to destroy all microbes (sterilization) on the applied surface. These agents can broadly be grouped under two categories, namely antiseptics and disinfectants, both serve the similar purpose but under different situations. In general, antiseptics are germicides applied on living (animate) surfaces (skin and mucous membrane) to suppress or prevent microbial infections; whereas, disinfectants are germicides usually applied to surfaces of inanimate objects. Sometimes the same compound may act as an antiseptic as well as a disinfectant and the action is dependent on the concentration of the drug, microbial load and exposure conditions. Antiseptics are also different from the antimicrobial antibiotics, in that the former exert antimicrobial action rapidly (usually at higher concentrations); whereas, an antibiotic produces its antimicrobial action relatively slowly and at a very low concentration. Antibiotics are used locally or topically or systemically, but the antiseptics are only applied topically on the skin and mucous membranes. Topically antiseptics are used in aseptic surgery, for antisepsis of the surgical site, surgeon hands, to treat local infections, in soaps and in teat dips. Disinfectants are used to disinfect surgical instruments and apparatus; hospital home or farm premises and in public health sanitation.

**Characters of an Ideal Antiseptic**:

i) Should have wide antimicrobial activity against all pathogens (bacteria, viruses, fungi and protozoa) and should be preferably cidal.
ii) Should be active even in the presence of blood, pus and tissue breakdown products.
iii) Should exert rapid and sustained germicidal action.
iv) Should not induce any untoward reaction in the host (nonirritating, nonallergic, nonstaining, noncorrosive or nontoxic).
v) Should not delay wound healing.
vi) Should be compatible with soap and detergents.
vii) It should be chemically stable, cheap and readily available.

A disinfectant in addition, should be able to penetrate crevices, cavities, films of organic matters, be easily washable and should not rust instruments.

**Mechanisms of Action of Germicides**:

i) Oxidation of microbial protoplasm (oxidizing agents, halogens and halogen derivatives).
ii) Denaturation of microbial proteins or enzymes (phenol derivatives, metals, alcohols).
iii) Interfering with the permeability of microbial cell membrane (detergents).

The potency of a germicide is generally expressed in terms of its **phenol coefficient** (or Rideal Walker coefficient). It is the ratio of the minimum concentration of the test chemical required to kill a 24 hour culture of *B. typhosa* in 7.5 min at 37.5 $^0$C to that of phenol under similar situations.

**Classification**: Based on chemical nature:

**Phenol Derivatives**: Used as antiseptics or disinfectants. These are protoplasmic poisons and denature proteins.

Phenol (carbolic acid): It is relatively a weak bacteriostatic at 0.1-1% and bactericidal or fungicidal at 1-2%; mainly used for disinfection of equipments or organic matter (at 3-4%) and not used as an antiseptic (as it is irritant, corrosive and cause systemic toxicity).

Cresol (cresylic acid): It is bactericidal. Cresol is a better disinfectant and less toxic than phenol. Used as 2% solution as a disinfectant for inanimate objects.

Both phenol and cresol are toxic to dogs and cats and should not be used to disinfect the kennels and cat cages.

Resorcinol: Its antimicrobial activity is similar to phenol. It is also keratolytic and antipruritic; used in seborrheic dermatitis in ring worm and eczema as 6% lotion.
Chloroxylenol (4.8%solution; dettol): Broad spectrum bactericide, used for surgical antisepsis. It is diluted with water (!:4) for skin sterilization, for cleaning of wounds and irrigation of uterus and vagina and for mouth wash (1%).
Hexachlorophene: Strong bacteriostatic against mainly Gram positive organisms, widely used in solid or liquid soaps for preoperative skin antisepsis.
Wood tar derivatives: Pine tar (antimicrobial action is due to presence of phenol derivatives). Guaiacol is the main constituent of creosote also used as expectorant and antitussive.

**Oxidizing agents**: These are short acting germicides, act by releasing nascent oxygen which oxidizes bacterial protoplasm.
Hydrogen peroxide (3%): It is used as an antiseptic on surface wounds and disinfectant in water treatment and for sterilization of dental and surgical instruments.
Benzoyl peroxide: It has antiseptic, keratolytic and antiseborrheic activity, so useful in treating pyoderma in dogs.
Sodium perborate: In aqueous solution it decomposes to sodium metaborate and hydrogen peroxide, which then gradually liberate oxygen. It is used as antiseptic in mouthwashes.
Potassium permanganate: It has broad spectrum antimicrobial action (bacteria, fungus and virus). A 1:5000 solution is used as antiseptic for irrigation of mucous membrane, cavities and wounds. It is also used to disinfect water. It stains the tissues and promotes rusting (not good for surgical instrument).
Peracetic acid: Recently introduced antiseptic and sterilizing agent, active against bacteria, fungi and viruses at 0.001- 0.003%, used in food industry, meat and poultry processing plants and dairies.

**Halogens**: These are used as topical antimicrobial agents. They bind with the protoplasm and oxidize proteins and interfere with vital metabolic functions of microbes.
Iodine: It is a potent, broad spectrum (bacteria, fungi, viruses) and rapidly acting microbicidal agent. At 50 ppm concentration it kills bacteria within 1 min and spores in 10 min. Tincture iodine (2% iodine) is used as antiseptic on skin (before surgical incision or hypodermic injections) and wounds. In large animals it is used as 7% solution. Lugols iodine (5% iodine) is used for irrigation of uterus in pyometra.
Iodophores (Povidone iodine): These are called iodine bearers. Povidone iodine is iodine with polyvinyl pyrrolidine used as a nontoxic, nonirritating and nonstaining general antiseptic; available as solution, spray or ointment containing 0.5-1% iodine.
Chlorine: A potent broad spectrum antimicrobial agent; kills most pathogens bacteria, viruses, fungi or protozoa. It is widely used to disinfect water supplies and inanimate objects and dairies. It is irritating to skin and mucous membrane.

**Chlorophores**: These include
Sodium hypochlorite: A 2- 5% solution is used to disinfect inanimate objects and 0.5% solution is used to irrigate dirty/suppurative wounds.
Calcium hypochlorite (contains 2-5% chlorine) used as disinfectant in serious infectious diseases (anthrax, tetanus, tuberculosis etc.)
Chloramine-T is bactericidal (releases chlorine), nonirritating, excellent for washing suppurative wounds, dairy equipment, bovine udder and milking machines.
Chlorinated lime (bleaching powder): A mixture of calcium hypochlorite and calcium chloride. It is kept airtight as it looses chlorine on exposure to air. It is effectively used to disinfect livestock quarters and water (in emergency).

**Biguanides**: These include
Chlorhexidine (savlon) is most important of this group. A powerful, nonirriating antiseptic; acts by disrupting bacterial cell membrane. It is more active against Gram positive organisms. It is one of the most common surgical and dental antiseptics.
Chlorhexidine gluconate as 4% emulsion is extensively used as skin cleanser by hospital personnel, preoperatively for surgical patient and care of wounds. In the form of 1% aqueous solution or 0.5% solution in 70% isopropanolol, it is used as general antiseptic and has been incorporated in ointments, skin and wound cleansers teat dips and shampoos. A 1% chlorhexidine acetate ointment is topically used as antiseptic for treatment of wounds in dogs, cats and horses.

**Surfactants**: These include
These chemicals reduce the surface tension of an aqueous solution and in veterinary medicine they are mainly used as antiseptics and disinfectants. Surfactants may be nonionic, anionic or cationic. The nonionic are not bactericidal. The anionic agents are active in mild acid solutions and include soaps, calcium mandelate and ammonium mandelate. Cationic detergents are active in alkaline medium and include mainly quaternary ammonium compounds. Both the surfactants are used as antiseptics. These act by denaturing bacterial proteins and alter bacterial cell membrane permeability by decreasing its surface tension. Their antibacterial activity is reduced in presence of blood, pus, serum and tissue debris.

Anionic surfactants: Soaps have antibacterial activity against Gram positive bacteria and acid- fast organisms. Soaps are used as antibacterial wash. The bacteria on the skin are suspended and washed out as a result of emulsification of lipoidal secretions that contain bacteria. The antibacterial potency of soaps is increased by inclusion of certain antiseptics (potassium iodide, hexachlorophene phenols etc). They are incompatible with cationic surfactants (as cation combines with anion of soaps, terminating action of both).

Cationic surfactants: These are a group of quaternary ammonium compounds. Benzalkonium chloride (aqueous solution of 1:5000-1: 10,000 is used for disinfecting of skin, mucous membranes, infected wounds and irrigation of eye or vagina). Benzathonium chloride is used as an antiseptic for skin and mucous membrane as 1:500 alcoholic and 1:1000 aqueous solutions. Cetylpyridinium chloride as a 1:100 aqueous solution is used for preoperative scrubbing of the intact skin and a 1:500 alcoholic solution is applied to the skin. They are adsorbed on the bacterial cell membrane and interfere with its permeability which resulting in bactericidal effect.

**Acids**: Hydrogen ion is bacteriostatic or cidal
Inorganic acid: Boric acid: A weak antiseptic (bacteriostatic); nonirritating to even delicate tissues. Its 2-4% aqueous solution is used as topical antiseptic in eye infections and as mouth wash. In the form of boroglycerine (31% w/v, boric acid in glycerine) it is used for treating FMD lesions. However, boric acid should not be used liberally on open wounds and mucous membranes as it is systemically toxic and causes vomiting, diarrhea and kidney damage.
Organic acids: Acetic acid: It is used in surgical dressings (1% solution), for irrigation of urinary tract (0.25%), to treat otitis externa (2-5%) and 5% to treat burn infections.
Benzoic acid and salicylic acid are used in dermatological preparations (Whitfield's ointment) as fungicidal and keratolytic agents.

**Alkalies**: Hydoxyl ions also have antimicrobial activity.
A 2% Soda lye (contains 94% sodium hydroxide) in boiling water is widely used to kill common bacterial pathogens such as those causing fowl cholera and pullorum disease. Calcium oxide/Lime when mixed with water produces calcium hydroxide, easily available, cheap disinfectant used to disinfect livestock premises. Its excess application on floor may cause dermal erosions and infections. Calcium hydroxide (mixed with 4 volumes of water and used as disinfectant in areas contaminated with excreta. Sulfurated lime topical solution is used as scabicide in veterinary medicine.

**Alcohols**:
Primary aliphatic alcohols are widely used antiseptics and disinfectants. They precipitate bacterial cytoplasmic proteins and the effect is related to their lipid solubility. Ethyl alcohol (70% ethanol) has strong antibacterial action (kills 90% bacteria within 2 min), but not against the spores. It is commonly used as skin antiseptic before surgical incision. As it is an irritant it should not be applied to mucus membrane or on delicate tissues. It is a poor disinfectant for instruments and promotes rusting. Isopropyl alcohol (Isopropanol 50%) has similar action to ethanol.

**Reducing agents**:
Formaldehyde (gas) and gluteraldehyde (oil) are used as disinfectants. They have potent germicidal properties against all microbes including spores and retain the activity even in the presence of organic matter. They are non corrosive to metals, paints and fabrics. Their solutions are highly irritating and caustic to the tissues.
Formalin (contains 37% formaldehyde gas in aqueous solution with methanol) is used as a fumigant disinfectant or disinfect spray for buildings. The combined solution of formaldehyde (10%) and phenol (5%) is used as disinfectant footbath.
Glutaraldehyde (1-2% alkaline solution in 70% isopropanol) used to sterilize surgical and endoscopic instruments and plastic and rubber apparatus.
Sulfur dioxide: A gaseous fumigant, produced by burning sulfur in closed areas. Its efficacy is maximum when the surfaces are moist as the gas dissolves in water to form sulfurous acid which is bactericidal. But it is corrosive to metals and fabrics.

**Heavy metals**:
Mercury compounds: The inorganic mercuric bichloride is an early mercurial antiseptic replaced by less irritant and less toxic organic mercurials like merbromin, thimerosal, nitromersol and phenylmercuric nitrate. The mercurials are weak antiseptics and act as bacteriostatic by inactivating SH enzymes of microbes. They are ineffective against spores. Their antiseptic or disinfectant use is greatly decreased because of environmental contamination.
Silver salts: These are microbicidal through astringent and caustic actions. The silver ion combines with SH, aminophosphates and carboxylic groups resulting in denaturation and precipitation of bacterial proteins. Silver nitrate (1:1000 aqueous solution) is a strong antiseptic and used for ophthalmic infection. Silver sulfadiazine is highly active against *Pseudomonas* and used on burns. Colloidal silver preparations slowly release nonirritating silver ions; used as mild antiseptic and in ophthalmic preparations.
Zinc salts (sulfate or oxide) are astringents, corrosive and used as mild antiseptics in the form of powder, ointment or lotion.
Copper sulphate: It has astringent, fungicidal and germicidal activities.

**Dyes**:
Azo dyes (Scarlet red, phenazopyridine hydrochloride) are effective against Gram negative organisms particularly in acidic medium. Scarlet red is commonly used as 5% ointment on sores, chronic ulcers and wounds. Phenazopyridine is used as urinary tract antiseptic, and in combination with sulfonamides in urinary tract infections.
Acridine dyes (Acriflavine hydrochloride, Proflavin sulphate): These are more active against Gram positive bacteria specially in alkaline medium. They are nonirritant and do not retard healing. The bandazes and gauze are impregnated with acriflavine gelly and extensively used for treatment of chronic ulcers and for burn dressing.
Gention violet: Active against *Staphylococci*, other Gram positive bacteria and fungi, but not against Gram negative bacteria and *Mycobacteria*. It is used as antiseptic (1% solution in 10% alcohol) in bed sores, chronic wounds and ulcers on mucous membranes, moist eczema and ring worm.

**Nitrofurazone** a nitrofuran derivative is bactericidal to both Gram positive and Gram negative, aerobic and anaerobic bacteria; acts by inhibiting enzymes of carbohydrate metabolism in bacteria. Its activity is reduced in the presence of serum. It is highly efficacious topically as 0.2% cream in burns and skin infections.

EXERCISE

**1. Write a short note on the following:**

a) Ideal antiseptic
b) Phenol derivatives
c) Biguanides
d) Surfectants
e) Chlorophores
f) Iodophores

**2. Differentiate between the following:**

a) Antiseptic and disinfectant
b) Iodophores and ionophores
c) Iodophores and Chlorophores
d) Anionic surfactant and cationic surfactant

**3. What do you mean by the following? Answer in one or two sentences for each. Define the following:**

a) Antiseptic
b) Disinfectant
c) Germicide
d) Sterilization
e) Sanitation
f) Iodophores
g) Chlorophores
h) Phenol coefficient
i) Rideal Walker Coefficient
j) Oxidizing agent
k) Surfectant
l) Guaicol
m) Fumigant
n) Boroglycerin
o) Whitfield's ointment

**4. Matching** (Parallel pairs)/**Multiple choices** (Correct choices):

a) Antiseptic: Resorcinol/Chlorohexinol/Hexachlorophene/Na hypochlorite/Chloramine-T/Chlohexidine/ Soap/Benzalkonium/Benzathonium/Cetylpryridinum/Boric acid/Acetic acid/Benzoic acid/Whitfield's ointment/Ethyl alcohol/Isopropyl alcohol/$ZnSO_4$/ZnO/Phenazopyridine/Acriflavin/Proflavin/Acridine dyes/Gentian violet/Boroglycerin
b) Disinfectant; Phenol/Cresol/Chlorine/Bleaching powder/Bleaching powder/Soda lye/Calcium oxide/Lime/Calcium hydroxide/Fomaldehyde/Gluteraldehyde
c) Chlorohexinol: Dettol
d) Chlorohexidine: Savlon
e) Buguanide: Chlorohexidine
f) Sulfurated lime: Scabicide
g) Silver sulfadiazine: Burns
h) Formalin: Fumigant/$SO_2$
i) $CuSO_4$: Astringent/Fungicide/Germicide
j) Guaicol:Antiseptic/Expectorant/Antitussive
k) Oxidizing antiseptic: $H_2O_2$/Benzyl peroxide/Na perborate/$KMnO_4$/Peracetic acid
l) Halogen antiseptic: Iodophores/Povidone iodine/Tr.iodine/Lugol's iodine
m) Chlorophore: Na hypochlorite/Ca hypochlorite/Chloramine-T/Bleaching powder
n) Anionic surfactant: Soap/Ca mandelate/Ammonium mandelate/Acid medium
o) Cationic surfactant: Alkaline medium/Benzalkonium/Benzathonium/Cetylpyridinum.

**5. Give most appropriate reason for each of the following statements:**

a) A true disinfectant cannot be used as an antiseptic.
b) Phenol is not recommended as an antiseptic
c) Wider the phenol coefficient, greater will be the disinfectant property.
d) Phenol/Cresol is not used for disinfecting kennels or cat cages.
e) Resorcinol is used in ringworm and eczema.
f) $KMnO_4$ is not used to disinfect surgical instruments.
g) Povidone iodine is called an iodophore.
h) Chloramine-T is called a chlorophore.
i) Anionic-cationic detergent combination should not be used in combination.
j) Soda lye in excess should not be used to disinfect floor of livestock sheds.
k) Alcohols should not be recommended to disinfect surgical instruments.
l) Mercurials are no longer recommended as antiseptics.

# CHAPTER – 38: ANTINEOPLASTIC DRUGS

Neoplasm or tumour is a mass of abnormal tissue that resembles the normal tissues in structure but it cannot fulfil any body functions and it grows at the expense of the body.It may be benign (encapsulated, do not cause metastases, do not recur if removed) or malignant (not encapsulated, mtastases and recur if removed). A normal cell turns into a cancer cell because of mutation in its DNA leading to either inactivation of tumour suppressor genes or activation of proto-oncogenes (normally control cell division and differentiation but can be converted to oncogenes) to oncogenes (confer malignancy). Normally, apoptosis (programmed cell death) sevre the purpose of self destruction of nonfunction/superannutated/abnormal cells (shedding of gastric mucosa, regression of mammaey myoepithelium durin dry period, aged blood cells etc). Anti-apoptopic genetic lesions induce cancer development.

**Cancer Biology**: Biology of cancer cells is important to understand the significance of various approaches and limitations of chemotherapy.

**Cell-cycle**: The difference between normal and cancer cells is primarily quantitative than qualitative ie have same biochemical processes but the rates are different. The activity of an anticancerous drug depends on its affinity to tightly bind to some cell constituents or affect processes that occur more rapidly in tumour cells. These processes in turn depend on the rate at which tumour cells move through the cell cycle.

The cell cycle is the progression of a dividing cell through state spanning the events from one mitosis to the next. $G_1$- is a presynthetic phase (variable duration), immediately follows mitosis, during which normal cellular events and protein and RNA synthesis occur in preparation for the S phase. During **S-phase** (8-20hrs) synthesis of DNA occurs. In **$G_2$ Phase** (3 hr in cancer cells) substituents required for mitosis are synthesized. In **M phase** (1 hr) mitosis occur; two $G_1$ cells are produced which either directly enter next cycle or into non-prolierative ($G_0$) phase (may be recruited any time in the cell cycle). The selectivity of anticancer drugs on cells is partially attributed to the difference in proportion of cells in the proliferative stage and the time required to complete a cell cycle.

**Principles of Cancer Chemotherapy**:

There are three main approaches to treat tumour or cancer: Surgical incision, irradiation and chemotherapy and the role of each of these depends on the type of tumour and the stage of development. Each of the modalities has strengths and limitations and hence combination of the approaches (multimodal therapy) is frequently employed to treat cancers. Surgery is ideal for localized, well circumscribed tumors and not limited by tumour size in contrast to chemotherapy but is limited by extension.Radiation is more appropriate than surgery for localized tumours in many locations (head and neck) where surgical intervention may lead to gross disfiguration, malfunction or extreme hazard. Effectiveness of radiation is not limited by tumour size although surgical debulking may facilitate therapy. Chemotherapy is ideal for disseminated cancers (as the agents are transported in blood), but its effectiveness is limited by the number of cancer cells ie the size of the tumour.

Chemotherapy is the main method of treatment for only a few cancers but it is increasingly used as an adjuvant to surgery and radiation. In malignant diseases, the objective of chemotherapy is either cure (when all cancer cells have been eradicated), remission (all clinical evidence has disappeared, but microscopic foci of cancer cells do exist) or palliation (remission of secondary signs without appreciable increase in survival time). The antineoplastic drugs either kill the neoplastic cells or modify their growth. However, the selectivity of these drugs is limited and most of them are very toxic. The effectiveness of antineoplastic drugs depends on to balance the antneoplastic activity and the toxicity of these drugs on host cells.

The antineoplastic drugs may be either cell cycle nonspecific (kill resting as well as dividing cells) or cell cycle specific (kill only actively dividing cells). $G_1$ phase specific vinblastine; S-phase specific methotrexate, 6-thioguanine, doxorubicin or 6- mercaptopurine; $G_2$ phase specific bleomycin and M-phase specific vincristine or vinblastine.

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The antineoplastic drugs are commonly administered in various combinations of drugs (combination chemotherapy). Increases anticancer activity, may reduce toxicity or lessen chance of development of drug resistance, dosages and timings. Each specific regimen is called 'protocol'. A protocol may use 1 or even the combination of 5 or 6 drugs depending upon the type of tumour, stage of malignancy, condition of the patient and financial constraints.

The antineoplastic agents are administered by oral, IV, IM, SC, intracavitary and topical routes and the choice depends on the individual drug and the location, size and type of the tumour.The dosages of antineoplastic drugs are generally calculated on the basis of body surface area (BSA) rather than body weight because of their narrow margin of safety. However, for small animals (dogs and cats) it is better to calculate the dose on the basis of body weight to avoid overdosage.

Most of the antineoplastic drugs are basically cytotoxic agents. Besides killing neoplastic cells they also act on some rapidly dividing or growing normal cells or tissues like bone marrow (Depression of bone marrow-resulting in granulocytopenia, agranulocytosis, thrombocytopenia and anaemia), RE system (lymphocytopenia and immunosuppression), epithelial linings (GIT complications, nausea, vomiting, ulcerative/haemorrhagic enteritis, stomatitis), Skin (alopecia due to damage of hair follicle), gonads (adversely affect spermatogenesis and ovulation), Fetus (abortion, fetal death , teratogenesis) and produce multiple side effects or toxicities. These drugs can also cause allergy or anaphylaxis and sometimes they themselves may be carcinogenic.

Study of biological effects of 'mustine' a nitrogen mustard chemical warfare agent (mustard gas) paved the way for development of anticancer drugs starting with cyclophosphamide (derivative of mustine).

**Classification of Anticancer Drugs:**

A. **Drugs Acting Directly on the Cells (Cytotoxic Drugs):**

**1. Alkylating agents:**

| | | |
|---|---|---|
| Nitrogen mustards (Derivatives of mustine) | : | Mechlorethamine, Cyclophosphamide, Chlorambucil and Mephalan |
| Ethylenimine | : | Thiotepa |
| Alkylsulfonate | : | Busulfan |
| Nitrosoureas | : | Carmustine, Lomustine and Streptozotocin |
| Triazene | : | Dacarbazine |

**2. Antimetabolites:**

| | | |
|---|---|---|
| Folic acid antagonists | : | Methotrexate |
| Purine antagonists | : | 6-Mercaptopurine, 6-Thioguanine and Azathioprine |
| Pyrimidine antagonists | : | 5-Fluorouracil and Cytarabine |

**3. Natural products:**

| | | |
|---|---|---|
| Cytotoxic Antibiotics | : | Actinomycin D, Doxorubicin, Daunorubicin, Mitomycin and Bleomycins |
| Enzymes | : | L-Asparaginase |
| *Vinca* Alkaloids | : | Vincristine, Vinblastine, Vindesine and vinorelbine |
| Epipodophyllotoxin | : | Etoposide |

**4. Miscellaneous Agents:**

| | | |
|---|---|---|
| Platinum complex | : | Cisplatin |
| Substituted urea | : | Hydroxyurea |
| Adrenocortical suppressant: | | Mitotane (Ortho para-DDD) |
| Taxanes | : | Placetaxel and Docetaxel (Docelatel) |
| Hydrazine | : | Procarbazine |

**5. Radioactive Isotopes:**

Sodium phosphate ($P^{32}$), Sodium iodide ($I^{131}$)

B. **Drugs Acting by Altering Tissue Hormonal Milieu**:

| | | |
|---|---|---|
| 1. Corticosteroids | : | Prednisone |
| 2. Estrogens | : | Diethylstilbestrol and Estradiol |
| 3. Progestins | : | Megestrol acetate |
| 4. Androgens | : | Testosterone |
| 5. Antiestrogen | : | Tamoxifen |
| 6. Thyroid hormone | : | Thyroxine |

**Alkylating Agents**

These compounds through formation of highly reactive carbonium ion intermediates transfer alkyl group (alkylation) to cellular macromolecules, particularly to DNA. Alkylation of DNA leads to miscoding and cross linking between DNA strands. The net result is interference with DNA transcription and replication, breaking of DNA strands and ultimately cell death. They have also radiomimetic property (actions on DNA resemble those of radiation).The adverse effect of alkylating agents include mutagenecity, depression of bone marrow, suppression of gonadal function, immunosuppression, GI disturbances and local vesication. The indications and doses of commonly used alkylating agents are as follows:

**Cyclophosphamide**: Widely used in veterinary medicine in combination with other drugs in acute lympholytic leukemia, lymphoma, sarcoma, carcinoma of lung, mammary gland and other organs (Dog & Cat: @ 50 mg/$m^2$ /day, orally or IV for 4 days).

**Mechlorethamine**: Lymphoreticular neoplasm, mast cell tumours (Dog & Cat: @ 5 mg/$m^2$ only IV as single dose or in 2-4 divided doses on successive days).

**Chlorambucil**: Chronic lympholytic leukemia, and lymphoma in dogs and man (Dog & Cat: @ 8 mg/$m^2$/day orally).

**Thiotepa**: Commonly used against solid tumours in dogs and cats (@ 0.2-9 mg/$m^2$, IV).

**Busulfan**: Use in myloid leukaemia; specific adverse effect pulmonary fibrosis (Busulfan lung).

**Mephalan**: Multiple myeloma and ovarian carcinoma (Dog & Cat: @ 0.1 mg/ kg daily for 10 days and then 0.005-0.1 mg/kg daily, orally or IV)

Streptozotocin: Has special affinity for beta-islets of Langerhans; used to induce diabetes and in the treatment of islet cell carcinoma (@35 mg/kg weekly for 4 weeks by slow IV).

**Antimetabolites**

These are analogs related to normal components of DNA or of coenzymes involved in the synthesis of nucleic acid. They competitively inhibit the utilization of normal substrate or get themselves incorporated forming malfunctional macromolecules.

**Folate Antagonists:**

**Methotrexate**: It inhibits dihydrofolate reductase required for synthesis of terahydrofolate, a cofactor essential for thymidylate synthesis which is essential for DNA synthesis and repair. Used in Malignant lymphoma, sertoli cell tumour, osteosarcoma, metastatic transmissible venereal tumour (Dog: @ 5 mg/$m^2$ orally on day 1 and 5 of each week.

**Pyrimidine Antagonists**

**5-Fluorouracil**: Converted in the body to a false nucleotide FDUMP (Fluorodeoxyuridine monophosphate) which inhibits thymidylate sythetase and blocks the conversion of deoxycytidilic acid to deoxythymidilic acid resulting into selective interference of DNA synthesis. It is used in GI, lung, liver and mammary carcinoma (systemic: @ 100-200 mg/ $m^2$ once weekly) and cutaneous carcinoma (topical: 5% cream).

**Cytarabine**: The triphosphate of cytarabine inhibits DNA polymerase and blocks generation of cytidilic acid leading to inhibition of DNA synthesis.It is indicated in acute leukemia in man and canine and feline lymphosarcoma (@ 100-150 mg/$m^2$ daily for 4 days slow IV or IM).

**Purine Antagonists:**

**6-Mercaptopurine** and **6-Thioguanine**: Highly effective antineoplastic agents, converted in the body to corresponding monoribonucleotides which inhibit the conversion of inosine monophosphate to adenine and guanine nucleotides. 6-Mercaptopurine is indicated in leukemia in dogs (@ 50 mg/$m^2$ daily, orally as tablet).

**Natural Products**

**Cytotoxic Antibiotics**:

**Actinomycin D** (Dactinomycin): An antibiotic produced by *Streptomyces* spp. A very potent antineoplastic agent; intercalates and forms stable complexes with the DNA, and thus prevents RNA transcription and protein synthesis. Also stabilizes the action of topoisomerase II. Mostly used in man in choriocarcinoma, testicular carcinoma, sarcoma, lymphoma (Dog & Cat: 1.5 mg/$m^2$, IV once weekly).

**Anthracycline antibiotics:** Doxorubicin (*Streptomyces pneuceiticus*), daunorubicin (*Streptomyces coeruleorubidus*): They intercalate and bind to DNA, disrupt helical structure and DNA template leading to inhibition of both DNA and RNA synthesis. But the main cytotoxic effect is due to stabilization of DNA topoisomerase II complex after the strand has been nicked. Indicated in solid tumours, lymphoma, sarcomas, carcinoma and leukemia (Dog & Cat: @ 20-30 mg/$m^2$,IV, every 3 weeks upto 6-7 doses).

**Bleomycins**: These are metal chelating glycopeptide antibiotics derived from *Streptomyces* spp. These possess potent antineoplastic action; chelate copper or iron, interact with oxygen and produce superoxide radicals that intercalate between DNA strands, causing fragmentation of DNA and also inhibition of its repair. Used in lymphomas, squamous cell carcinoma (@ 10 mg/$m^2$, IV, IM or SC once daily for 3-4 days followed by once weekly up to a maximum cumulative dose of 200 mg/$m^2$).

**Miomycin**: It is derived from *Streptomyces caespitosus*; acts like alkylating agents. It cross-links DNA and also breaks DNA through free radical production. It is used in myeloid leukemia and Hodgkin's disease. Its toxic effects include myelosuppression, renal damage and fibrosis of lungs.

***Vinca* Alkaloids**: Vincristine, vinblastine, vindisene and vinorelbine. Source: *Catharanthus roseus* (Periwinkle plant).These are mitotic inhibitors, bind with microtubular protein 'tubulin', inhibiting its polymerization into microtubules, thus preventing spindle formation. The chromosome fails to move apart during mitosis, causing metaphase arrest. They are relatively non toxic agents and widely used in veterinary medicine in combination with others against lymphoreticular neoplasms, carcinomas, sarcomas, transmissible venereal tumours, CNS tumours. Dose: Vincristine (@ 0.5 mg/$m^2$, IV, weekly or biweekly); Vinblastine (@ 2 mg/$m^2$, IV, weekly or biweekly). Vinorelbine has active metabolites and can be administered orally.

**Etoposide**: A semisynthetic derivative of podophyllotoxin, plant glycoside of mandrake root (*Pdophyllum peltatum*); acts on G2 phase causing breaks in DNA by stimulating topoisomerase II. Used in testicular, bladder or lung cancer and lymphoma.

**Taxanes**: Paclitaxel obtained from the bark of western yew tree and docelatel (analog of paclitaxel). These act by interfering with mitosis.These enhance polymerization of tubulin to microtubules, form a stable complex with microtubules after forming a stable complex and prevent depolymerization of microtubules (causing imbalance in tubulin and microtubule dynamic equilibrium) Used in treating ovarian and breast cancer. Their toxicity is due to bone marrow suppression and cumulative neurotoxicity.

**Enzymes**:

**L-Asparaginase** (Crisantaspase): The malignant cells cannot synthesize an essential growth factor L-asparagine (as deficient in L-asparagine synthetase enzyme) and therefore depend on exogenous supply of L-asparagine formed by the normal cells. L-asparaginase (from *E.coli*) breaks asparagine (to aspartic acid and ammonia) thus deprives the malignant cells of aspragine (depleting the nonessential aminoacid in the host). It is used in acute lympholytic leukemia and lymphoma (Dog & Cat: 10,000-30,000 iu/$m^2$, IV or IP once weekly). It may cause severe allergic reaction).

### Miscellaneous Agents

**Cisplatin**: A platinum compound; hydrolyses intracellularly to yield a diamine platinum complex, which reacts with protein and nucleic acid, cross linking between DNA strands and between DNA and proteins and also has radiomimetic property. It is very effective against testicular and ovarian carcinoma. It is highly nephrotoxic.

**Hydroxyurea**: It is an urea analog; inhibits ribonucleotide reductase, thus interfering with the conversion of ribonucleotides to deoxyribonucleotides and blocks DNA synthesis. Used in polycythemia vera in man (increase in number of circulating RBC) and granulocytic leukemia in dogs (50 mg/kg/day, orally).

**Mitotane** (Orthopara DDD, dichlorodiphenyldichloroethane): Closely related to DDT, destroys adrenal zona fasciculata and zona reticularis (adrenocortical suppressant) and used in adrenal carcinoma (50 mg/kg orally daily for 4-7 days, then once weekly).

**Paclitaxel**: A diterpine obtained from bark of the Western Yew tree, exert cytotoxic action by interfering with functioning of tubulin (tubulin-microtubule dynamic equilibrium is essential for mitotic functions). It enhances the polymerization of tubulin, a mechanism opposite to that of vinca alkaloids. It is indicated in ovarian and breast carcinoma.

**Procarbazine**: It forms alkylating intermediates or free radicals that cause DNA damage and inhibition of protein, DNA and RNA synthesis. It is used in lymphoreticular tumour (Dog: @ 100 mg/$m^2$ orally, once daily for 4-6 weeks). It is an inhibitor of MAO (Contraindications: Adrenaline (enhanced hypertension) and cheese or liver (contain MAO: increase metabolism of procarbazine).

**Radioactive isotopes**: Radioactive Sodium iodide ($I^{131}$) is used for treating metastatic thyroid tumour and sodium phosphate ($P^{32}$),) and sodium iodide ($I^{125}$) are also used in the therapy of certain tumours. Their cytotoxic effect is due to ionizing radiations, which damage DNA, disrupt cellular metabolism and ultimately kill the cells.

### Hormones/Hormone Antagonists:

**Prednisone**: It is used against lymphoreticular neoplasms, mast cell and brain tumours. Dose: @ 10-40 mg/$m^2$ orally once or twice daily, gradually decreased to 10-20 mg /$m^2$ on alternate days.

**Estrogens**: Blocks the effect of androgens in androgen dependent prostatic tumours, and they are also used in mammary cancer therapy with other drugs (to recruit resting mammary cancer cells into proliferating cells thus allowing a greater killing efficacy of cytotoxic drugs given with them).

**Megestrol acetate**: Estrogens increase the risk of endometrial carcinoma and progestins block this effect (Dose: Cat: 0.5 mg/kg, orally daily for 2 weeks, then twice weekly).

**Androgens**: Block the effect of estrogens and are used in mammary gland carcinoma (after using tamoxifen) and nephroma and also to stimulate erythrocyte formation (has erythropoietin stimulating property).

**Tamoxifen**: Effective in hormone dependent breast cancer. In breast tissue it competes with endogenous estrogens for the estrogen receptors and inhibits the transcription of estrogen responsive genes (dose: 40 mg /$m^2$ every 12 hrs orally for 1 week then 10 mg /$m^2$ every 12 hrs thereafter.

Androgen antagonists: Flutamide and cyproterone are used against prostate carcinoma.

Thyroid hormones: Are effective against some metastases of papillary carcinoma.

## EXERCISE

1. Classify anticancer drugs and discuss the principles of cancer chemotherapy
2. Classify the antineoplastic agents of natural origin and discuss in brief their mode of action.
3. Enlist the alkylating anticancer drugs and discuss their mode of action.
4. **Wrie a short note on the following**:
   a. Principles of cancer chemotherapy
   b. *Vinca* alkaloids
   c. Vegetable anticancer agents
   d. Anticancer antibiotics
   e. Alkylating anticancer drugs
   f. Antimetabolite anticancer drugs
   g. Apoptosis and anticancer therapy
   h. L-Asparaginase
5. **Describe the mechanism of action of the following drugs**:
   a. Cyclophosphamide
   b. Dactinomycin

c. Methotrexate
d. 5-Fluorouracil
e. Cytarabine
f. Thioguanine
g. Mercaptopurine
h. Daunorubicin
i. Bleomycin
j. Mitomycin
k. L-Asparaginase
l. Crisantaspase
m. Paclitaxel
n. Docelate
o. Etoposide
p. Vincristine
q. Taxanes
r. *Vinca* alkaloids

6. **Give the source of the following**:
a. *Vinca* alkaloids
b. Dactinomycin
c. Doxorubicin
d. Bleomycins
e. L-Asparaginase
f. Mitomycin
g. Taxanes
h. Paclitaxel
i. Etoposide

7. **Matching (Parallel pairs)/Multiple choices (Right choices)**:
a. Alkylating anticancer: Mechloethamine/Cyclophosphamide/Dactinomycin/Chlorambucil/Mephlan/Thiotepa/Busulfan/Carmustine/Dacarbazine/Streptozotocin
b. Antimetabolite anticancer: Methotrexate/Mercaptopurine/Thioguanine/Azathioprine/Cytarabine/5-FU
c. Folic acid antagonist: Methotrexate
d. Purine antagonist: Mercaptopurine/Thioguanine/Azathioprine
e. Pyrimidine antagonist: 5-Fluorouracil/Cytarabine
f. Cytotoxic antibiotic: Dactinomycin/Doxorubicin/Bleomycin/Mitomycin
g. Anticancer enzyme: L-Asparaginase/Crisantapase
h. *Vinca* alkaloid: Vincristine/Vinblastine/Vindesine/Vinorelbine/*Cathranthus roseus*/Periwinkle plant/Sadaphuli
i. DDD/Mitotone: Adrenal carnicoma/Adrenocortical suppressant
j. Procarbazine: Anticancer drug with MAO inhibition
k. Alkylating anticancer: Miscoding of DNA/Cross-linking of DNA strands/Inhibition of DNA transcription/Inhibition of DNA replication/Radiomimetic/Mutagenecity/Immunosuppression/DNA breaks
l. Methotrexate: Dihydrofolate reductase inhibition/Intefers with formation of tetrahydrofolate/interferes with synthesis of thymidylate /Interfers with DNAformation
m. 5-FU/Cytarabine: Fradulent nucleotide/FDUMP/Thymidylate synthetase inhibition/Prevents conversion of deoxycytidilic acid to deoxythymidilic acid/DNA inhibition
n. 6-Mercaptopurine/6-Thioguanine: Fradulent nucleotide/Inhibition of formation of adenine nucleotides/Inhibition of guanine nucleotide
o. Bleomycin: Glycopeptide antibiotic/Chelate Cu and Fe/Superoxide formation/Intercalation of DNA strands/Fragmentation of DNA
p. Anthracycline antibiotic: Doxorubicin/Daunorubicin/Intercalates DNA strands/Inhibition of RNA synthesis/Stabilization of DNA topoisomerase II complex/Anticancer action
q. Mitomycin: Anticancer antibiotic/Breaks DNA/superoxide formation
r. Etoposide: Podophyllotoxin/Mandrake root/*Podophyllum peltatum*/Stabilization of topoisomerase II/Anticancer
s. Taxanes: Paclitaxel/Docelatel/Freezes tubule/Mitosis arrest/Bark of Western yew tree/Anticancer

8. **Substantiate each of the following statements by giving the most appropriate reason or explanation**:
a. Anticancer drugs have low margin of safety.
b. Anti-apoptopic lesion induces cancer.
c. Cancer chemotherapy is not apoptosis
d. Streptozotocin induces diabetes.
e. Crisantapase exerts anticancer action
f. L-Asparaginase is an anticancer enzyme
g. Oestrogens are used in prostrate cancer.
h. Vincristine is a anticancer drug
i. Paclitaxel acts in contrast to vincristine
j. Isotopes exert cytotoxic action
k. Anticancer drugs cause mutagenecity
l. Anticancer drugs cause teratogenecity
m. Anticancer antimetabolites block cell division
n. Multi-drug therapy is followed in cancer therapy
o. Chemotherapy is ideal for dessiminated cancer
p. Cytotoxic antibiotics are used as anticancer drugs
q. Antioestrogens/Androgens/Tamixifen are/is used to treat mammary gland carcinoma.
r. Flutamide/Cyproterone is used in treating prostrate carcinoma.
s. 5-Fluorouracil/Cytarabine cause thymineless death of cancer cells.
t. Animal receiving procarbazine should not be fed cheese/meat or administered adrenaline.
u. Anticancer chemotherapy renders the patient prone to infections.
v. Multi modal approach is followed in treating neoplasic diseases.
w. Dosage of anticancer drugs is calculated based on body surface area rather than body weight.
x. Alkylating anticancer drugs/Cyclophosphamide interfere (s) with DNA transcription and replication.
y. Most of the anticancer drugs cause immunosuppression/aplastic anaemia/gonadal hypofunction.
z. Western yew tree/Sadaphuli/Mandrake root have therapeutic value.

* what are the characteristic of ideal anthelmintics ... mechanism of Action of Anthelmintics.

# Chapter – 39: TREATMENT OF WORM INFESTATION

## 1. Anthelmintics:

### General Considerations

Helminthic infection (gastrointestinal parasitism) in animals is very common and it is responsible for considerable losses to the livestock industry, mainly because of slow and poor growth and development of affected animals. However, severe helminthic infection sometimes causes even death of animals. The most common helminths of domestic animals are nematodes (roundworms), cestodes (tapeworms) and trematodes (flukes). A large number of anthelmintics (antiparasitic drugs) have been developed to kill or to lower worm burden in animals.

The term anthelmintic is an elision of anti and helminth. The nematodes, cestodes and trematodes are collectively known as helminths. Drugs that are effective against any one or all three groups of helminths are termed as anthelmintics.

**a. Classification of Anthelmintics:** Based on type of helminths against which they are effective:

Antinematodal drugs: Drugs effective against the nematodes or roundworms **(R)**.

Anticestodal drugs: Drugs effective against the cestodes or tapeworms **(T)**.

Antitrematodal drugs: Drugs effective against the trematodes or flukes **(LF)**.

| Group | Name of the Drug | Anthelmintic Activity Agianst |
|---|---|---|
| Benzazepines | Epsiprantel | Cestodes (Dog & Cat) |
| Benzimidazoles | Albendazole | GI Nematodes, cestodes & trematodes (adult) |
| | Cambendazole | GI Nematodes (Pig & Bird) & cestodes (Pig & Bird) |
| | Fenbendazole | GI Nematodes (All spp) & cestodes |
| | Flubendazole | Nematodes (Pig) |
| | Luxabendazole | GI Nematodes (Sheep mainly) & trematodes |
| | Mebendazole | GI Nematodes (All spp) & cestodes (adult & larvae) |
| | Oxfendazole | GI Nematodes (All spp) & cestodes |
| | Oxibendazole | GI Nematodes (Horse mainly) |
| | Parbendazole | GI Nematodes & Lungworm (in all farm animals) |
| | Thiabendazole | GI Nematodes (All farm animals) & trematodes (adult) |
| | Triclabendazole | Trematodes (LF day old to mature in all farm animals) |
| Benzimidazole Prodrugs | Febantel | GI Nematodes (All spp) & cestodes |
| | Netobimin | GI Nematodes (also larvae), cestodes & trematodes |
| | Thiophanate | GI Nematodes (All farm animals) |
| Halogenated Hydrocarbons | Carbon tetrachloride | Trematodes (LF, Adult in sheep) |
| | Hexachloroethane | GI Nematodes & trematodes (LF, adult) |
| | Hexachloroparaxylene | Trematodes (LF, adult, all farm animals) |
| | Tetrachlorodifluoroethane | Trematodes (LF, adult, sheep) |
| | Tetrachloroethylene | GI Nematodes (All spp) |
| Heterocyclic Compounds | Diethylcarbamazine | Nematodes (heartworm, preventive) |
| | Phenothiazine | GI Nematodes (Farm animals, Strongyles in horse) |
| | Piperazine | GI Nematodes (All spp, Ascaraiasis) |
| Hydroxynilides | Resorantel | Cestodes & Paramphistomes (ruminants) |
| Imidazothiazoles | Butamisole | GI Nematodes (dog) |
| | Levamisole (Tetramisole) | GI Nematodes & Lungworm:larval/immature, all spp) |

| | | |
|---|---|---|
| Macroocyclic Lactones | Avermectins:<br>Abamectin<br>Doramectin<br>Ivermectin | In all species (oral & SC)<br>Nematodes & ectoparasites<br>Nematodes & ectoparasites<br>Nematodes & ectoparasites |
| | Milbemycins:<br>Milbemycin D<br>Milbemycin oxime<br>Moxidectin | <br>Nematodes (heartworm preventive) in dog<br>Nematodes (heartworm preventive) in dog<br>Nematodes & ectoparasites in cattle |
| Organic Phosphates | Coumaphos | GI Nematodes & Ectoparasiticide (all farm animals) |
| | Crufomate | GI Nematode & Ectoparasiticide (all farm animals) |
| | Dichlorvos | GI Nematodes (Dog, cat, pig & horse) |
| | Haloxon | GI Nematodes (all farm animals) |
| | Naphtholphos | GI Nematodes (all farm animals) |
| | Trichlorphón/Dipterex | GI Nematodes & Ectoparasiticide (all farm animals) |
| | Uredophos | GI Nematodes & Cestodes (dog: *D. caninum* & cat) |
| Quarternary Ammonium Compounds | Bephenium | GI Nematodes (Ruminants, dog & cat) |
| | Thenium | GI Nematodes (Mature/immature hookworms in dog) |
| Quinolines | Praziquantel | Cestodes(all stages)&Schistosomes,farm/zoo animals |
| Substituted Phenols | Bromosalans | Trematodes (adult/juvenile LF in ruminants) |
| | Diamfenetide | Trematodes (Immature LF in sheep) |
| | Dichlorophen | Cestodes (dog,except *Echinococcus*, cat & sheep) |
| | Disophenol | GI Nematodes (hookworm, injectable in dog & cat) |
| | Hexachlorphene | Cestodes & Trematodes (adult LF in ruminants) |
| | Niclofolan | Trematodes (adult/immature LF in ruminants & pig) |
| | Nitroxynil | Adult LF, Nematodes (gapeworm in birds) & *O. ovis* |
| | Nitroscanate | Cestodes & Nematodes (dog only) |
| Sulfonamides | Clorsulon | Trematodes (adult/young LF in ruminants) |
| Tetrahydropri-midines | Morantel | GI nematodes: mature/immature (all spp),cattle *Thelazia* also |
| | Oxantel | GINematodes (dog whipworm) |
| | Pyrantel | GI Nematodes:mature/immature (all spp) dog pinworm |
| Miscellaneous Compounds | Arecoline | Cestodes (dog & cat) |
| | Bunamidine | Cestodes (dog & cat) |
| | n-Butyl chloride | GI Nematodes (dog & cat) |
| | Dithiazanine iodide | Nematodes (heartworm: microfilariae) |
| | Hygromycin B | GI Nematodes (pig & birds) |
| | Lead arsenate | Cestodes (Young ruminants) |
| | Stannous chloride/oxide | Cestodes (dog & birds) |
| | Thiacetarsamide | Nematode (heartworm: adult) |
| | Toulene | GI Nematodes (hookworm dog & cat) |

**b. Ideal Anthelmintic:**

i. Should have **high efficacy:** The drug must exhibit high level of antiparasitic action. If a drug eliminates 95% of GI nematode burden from ruminants, it is said to have good efficacy. But its efficacy is poor if it eliminates only 70%. An efficacy of 100% for all stages of parasite is not necessarily a desirable effect, since this totally eliminates the source of antigenic stimulation by the organism and may weaken the animals acquired resistance to the parasite.

ii. Should have **broad spectrum** of activity against both mature and immature parasites including larvae.
iii. **Wide therapeutic index.**
iv. **Easy to administer** to large number of animals.
v. Should not exceed approved **limits of drug residue** or should not require long withdrawal period because of residue(s).
vi. Should be **economic**.

**c. General Mode of Action of Anthelmintics:** Most anthelmintics can be classified into two major categories on the basis of their mechanism of actions:

**Drugs affecting the energy production of the parasites:** Biochemical reactions associated with the energy production of the parasites are the most important sites of drug action. On the basis type of biochemical reactions interrupted the anthelmintics are grouped as follows.

a) **Inhibitors of fumerate reductase enzyme and mitochondrial reactions:** In some anaerobic helminthes (*Ascaris*) the formation of ATP (required for muscular contraction) involves reduction of fumerate to succinate by the enzyme fumerate reductase in the mitochondria. This reaction helps to reoxidize NADP to form ATP. Some drugs inhibit fumerate reductase enzyme action, thus block the generation of ATP and resulting in muscular paralysis and eventual death of the parasite: Benzimidazoles (except mebendazole, flubendazole and triclabendazole), benzimidazole pro-drugs, levamisole, bithionol, hexachlorophene.
b) **Inhibitors of tubulin polymerization and glucose uptake:** These drugs bind to free beta-tubulin, inhibiting its polymerization and thus interfering with microtubule–dependent glucose uptake. In absence of glucose there is depletion of the worm's glycogen reserve, which renders its unable to produce ATP necessary for survival. Some benzimidazoles like mebendazole and flubendazole primarily act by inhibiting glucose transport but these two do not inhibit fumerate reductase system.The primary site of action of cambendazole and fenbendazole is fumerate reductase inhibition. In addition, like mebendazole and flubendazole they also inhibit glucose transport. This explains their effectiveness against certain parasites that lack fumerate reductase system. The heartworm microfilaricide, dithiazanine also act by inhibiting the **glucose uptake** by the parasite but the exact mechanism of inhibition of glucose uptake is not known.
c) **Inhibitors of electron transport mediated oxidative phosphorylation in the mitochondria of the parasites:** These drugs interfere with the electron transport in the mitochondria and thereby inhibit the oxidative phosphorylation and generation of ATP. The fumerate is converted to succinate but ATP is not produced. These drugs are mainly effective against flukes and tapeworms. These drugs are not effective against roundworms, inspite of having similar mitochondrial phosphorylation system because the drugs cannot penetrate tissues of the intact roundworms. These drugs also uncouple oxidative phosphorylation in the mitochodria of mammals and are often fairly toxic (Salicylanilides, substituted phenols and halogenated hydrocarbons: niclosamide, clioxanide, oxyclozanide, rafoxanide, closantel, resorantel; bithionol, disophenol, dichlorophen, hexachlorophene, niclofolan, nitroxynil, nitroscanate, bromosalans; carbontetrachloride etc).
d) **Inhibitors of glycolysis:** These drugs are either organic heavy metal compounds or other chemicals, have tendency to bind with the sulfhydryl (- SH) groups and thereby alter the structure of proteins and the active sites of glycolytic enzymes (phosphoglycerate kinase and phosphoglycerate mutase) of the parasite and host (Arsenicals: Thiacetarsamide; Antimonials: Potassium antimony tartarate and stibophen and antitrematodal sulfonamide: Clorsulon).

**Drugs Affecting the Neuromuscular System of the Parasites, thereby Causing Paralysis:**

Neuromuscular system may be affected by inhibiting the destruction or by mimicking/enhancing or antagonizing the action of neurotransmitters .The ultimate result is either spastic or flaccid paralysis of the parasite and the paralysed parasite is expelled by the normal peristaltic movement of the host. The drugs affecting neuromuscular system are classified as below:

b) **Cholinergic agonists:** These drugs affect the neuromuscular system of the parasite by acting as cholinergic agonists: Nicotine-like action, stimulating and subsequently blocking the neuromuscular junctions, resulting sustained muscle contraction and spastic paralysis of nematodes (Imidazothiazoles: Butamisole, tetramisole and levamisole; Pyrimidines: Morantel, oxantel and pyrantel; Quaternary ammonium compounds: Bephenium and thenium etc.

c) **Anticholinesterases:** ACh is also a neurotransmitter in parasites just like in higher animals. The enzyme AChE also present in the parasite destroys ACh and thus prevents over stimulation of smooth muscles. These drugs cause inhibition of acetyl cholinesterase (AChE) enzyme followed by constant depolarization due to accumulation of excess ACh at the neuromuscular junction. This leads to interference with neuromuscular transmission and consequent paralysis and expulsion of the parasite, through enhanced intestinal peristalsis. The relative safety of OP compounds (Coumaphos, haloxon, dichlorvos etc) for the host is probably related to lack of susceptibility of host AChE to the drug.

d) **Muscle hyperpolarizers:** An anticholinergic action at the myoneural junction in worms, producing competitive or non-depolarising type of neuromuscular blockade like curarae. This results in hyperpolarization of the muscle membrane of the worm leading to flaccid paralysis, facilitating its expulsion (Piperazine and avermectins).

e) **Potentiation of inhibitory neurotransmitters (GABA agonists):** The normal function of GABA in mammals and invertebrates is inhibition of neurotransmission. These drugs act by potentiation of GABAergic transmission (opening of chloride channels) between nerve and muscle. Potentiation of GABA leads to hyperpolarisation of postsynaptic cells leading to interference with neurotransmission to muscles and cosequent muscular paralysis (Ivermectin, abamectin, doramectin, moxidectin, milbemycin oxime and also piperazine).

**Other actions:** Besides above some of the anthelmintics produce their effect by other actions.

a) **Drugs affecting parasite reproduction:** Low level of feeding of these drugs to animals constantly inhibit the egg production of the parasites remaining in the digestive tract of the host and thereby reduce the pasture contamination by helminth eggs, an important control measure in cattle and sheep management (Phenothiazine and benzimidazoles).
b) **Drugs affecting the permeability of the cells and cause vacuolation of the tegument** (praziquantel and diamfenetide).
c) **Drugs cause disruption of tegument of parasites**: Bunamidine, epsiprantel and praziquantel.
d) **Drugs act by unknown mechanism:** Bitoscanate, paromomycin, phenothiazine and triclabendazole.

**d. Anthelmintic resistance:** Resistance to anthelmintics by the worms develops somewhat slowly in comparison to antibiotic resistance in bacteria. However, the development of resistance by nematodes to different groups of anthelmintics is becoming widespread (resistance to benzimidazoles, levamisole and avermectins by roundworms of cattle, sheep, goat and horses). Continuous use of a highly effective anthelmintic results in selective removal of the most susceptible genotypes resulting in succeeding resistant progeny. The resistance is manifested by passage of increased number of parasite eggs, higher establishment rates of adult worms in the host and greater number of larvae on the pasture after treatment than would occur if the parasites were susceptible to the antiparasitic drug. Cross-resistance may also occur between drugs having similar mode of action (benzimidazoles). Anthelmintic resistance can be prevented by:

a) Designing management practices to reduce exposure to parasites and to minimize the frequency of use of anthelmintics.
b) Development of resistance can be delayed by slow rotation of different chemicals with different mechanisms of action.
c) Planning treatment of whole herd/flock at a time.
d) By taking proper control measures against the parasitic phase in the host at proper time and to the free living, nonparasitic stages in the environment.

## 2. Antinematodal Drugs

**Classification:**

a) Simple heterocyclic compounds
b) Benzimidazoles/Benzimidazole prodrugs
c) Imidazothiazoles
d) Tetrahydropyrimidines
e) Organophosphorous compounds
f) Macrocyclic lactones
g) Drugs used in the treatment of heartworm in dogs
h) Miscellaneous antinematodal compounds

### a. Simple Heterocyclic Compounds

**Piperazine and its Derivatives:**

**Chemistry:** Chemically piperzine is diethylenediamine. It is a strong base, very unstable and consequently easily absorbs water and carbon dioxide; thus containers should be tightly closed and protected from light. The simple salts of piperazine (piperazine adipate, citrate, phosphate, sulphate, tartrate and hydrochloride) are more stable and are used. The antiparasitic action of different salts of piperazine is mainly due to the piperazine base.

**Anthelmintic spectrum:** All the derivatives of piperzine have similar efficacy. They are good for ascarid and nodular worm infections of all the species of domestic animals (100% efficacy), moderate for pinworm (Oxyuris sp.) infections, variable effect on other worms like hookworms and strongyles but no effect on whipworms (Trichuris sp), tapeworms and flukes. They have a wide margin of safety in all domestic animals.

**Pharmacokinetics:** Piperazine compounds are readily absorbed from the upper part of the GI tract, partly metabolized in the tissues and the remainder is excreted in urine within 24 hours.

**Mode of action:** The anthelmintic action of piperazine compounds is due to

a) Anticholinergic action at the myoneural junction in worms, producing a competitive or non-depolarising type of neuromuscular blockade like curarae.
b) Blockade of succinic acid production by the worm.
c) Reversible inhibition of neuromuscular transmission in the worm by acting like GABA, the inhibitory neurotransmitter on GABA gated chloride channels in nematode muscle.

The end result is the flaccid paralysis of the worm. Worms lose motility and thus ability to maintain their position in the intestinal tract. They are passively swept along by intestinal peristalsis and voided live in the feces. Purgation is not generally advised when piperazine is used.

**Administration:** Piperazine compounds are administered orally, usually in the feed (adipate or citrate salts) or drinking water (hexahydrate) over a 2-day period. In horses the drug is administered by stomach tube. Dogs and cats are usually dosed with tablets.

**Dosage:** Doses of piperazine compounds are expressed in terms of the amount of piperazine base.

Horses: 110 mg/kg; Swine, cattle, sheep and goats: 110 mg/kg; Dogs and cats: 45-65 mg/kg; Poultry: 32 mg/kg (about 0.3 gm for each adult bird) given each of 2 successive feedings or in drinking water for 2 days.

**Safety and toxicity:** The toxicity is normally very low. Sometimes neurotoxicity (incoordination, head pressing) and emesis occur in small animals at higher doses. The drug can be administered to pregnant animals and also to those animals suffering from gastroenteritis.
**Contraindications:** No known contraindications except in long standing renal or liver diseases. In heavy ascarid infections, treatment with piperazine or OP compounds results in intestinal blockade and rupture due to expulsion of large masses of worm simultaneously. Benzimidazoles are preferred in treating such cases because the death of worms is slow and expulsion is delayed. Piperazine and oxantel are mutually antagonistic.

**Phenothiazine:**
It was synthesized in 1885 and was one of the early drugs with a wide range of activity against gastrointestinal nematodes. It was extensively used in cattle, sheep, goats, horses and chickens. Development of truly broad-spectrum anthelmintics in 1960 has reduced the use of phenothiazine. It is now primarily used in continuous low level feeding programme for ruminants and for formulation of mixtures with other drugs for broader spectrum. It is still used in horses. Its toxicity has limited its use in swine and totally prevented its use in dog, cat and human.
**Chemistry:** Chemically it is thiodiphenylamine. The pure compound is a pale, green yellow powder, insoluble in water, stable when dry but oxidizes when wet.
**Anthelmintic spectrum:** The drug has a wide range of activity against gastrointestinal nematodes and mainly used in ruminants and horses. The drug possesses good anthelmintic activity against stomach worms of ruminants (*Haemonchus contortus*, *Ostertagia* spp., *Trichostrongylus axei*), nodular worms (*Oesophagostomum* spp.) of ruminants and swine, hookworms (Bunostomum) and small intestinal nematodes. Despite the greater sensitivity of horses than ruminants to phenothiazine poisoning, the drug is still used in equine because of its excellent efficacy against Strongyles. The drug is ineffective against equine ascarids and bots. The drug is effective against caecal worm of chickens and turkeys (*Heterakis gallinarum*). The drug is not effective against parasitic larval stages or immature adult worms of any of the ruminant parasites except immature forms of *Haemonchus*, which are effectively removed. It has no action against flukes and tapeworms.

**Mode of action:** The exact mechanism by which phenothiazine destroys the worm is not known, but may be due to:

a) Inhibition of certain vital enzymes (succinoxidase, glyoxalase, cholinesterase etc.) in the tissue cells of the parasites.
b) The drug affect the parasites reproduction and low level of feeding of the drug to animals inhibit the egg production of the parasite remaining in the GI tract of the host, ultimately reduce the pasture contamination by the helminth eggs, forms the basis of control measure in cattle and sheep management.

**Pharmacokinetics:** Following oral administration the drug is converted to phenothiazine sulfoxide by the cellular enzymes of the intestinal epithelium and absorbed. After absorption phenothiazine sulfoxide is further oxidized in the liver to two colorless substances, leucophenothiazone and leucothionol and excreted in urine. These products are again oxidized in the atmosphere to brown-red dyes, phenothiazone and thionol, which discolors the urine and milk of the animals for several days.
**Administration:** Phenothiazine is insoluble in water so bentonite (colloidal aluminium silicate) is used to keep the drug in suspension and it should be shaken prior to dosing animals. In ruminants, it is administered orally as a single drench once in a month. Powdered phenothiazine is added to the feed generally for prophylaxis. Fowls are treated with single dose of the drug in feed for a 1-day treatment once a month for control of caecal worm infections.
**Dosage:** Single dose treatment
Sheep and Goats: > 27 kg: 25-30 gm; 11-23 kg: 12.5 gm; Cattle: 10 gm/45 kg (maximum 70 gm); Calves:

Minimum 10gm; Horses: 3-5 gm/45 kg (administer half of the dose for 2 days); Chickens: 0.5 gm/bird; Turkey: 1gm/.bird.
**Daily prophylactic treatment:** Sheep and Goats: 0.25-0.5 gm/animal; Cattle: 0.5 gm/45 kg; Horses: Adults: 2-5 gm; colt: 1 gm.

**Toxicity:** The toxicity of phenothiazine varies among different species. Sheep, goats and birds are most resistant to toxic effect. Cattle and swine are more susceptible. Horses are most susceptible. Dogs and cats are easily poisoned and so never used in these animals. Toxic signs in horses include dullness, weakness, aNorAxia, oliguria, colic constipation, fever and signs relating to haemolysis of RBC like icterus, anaemia, haemoglobinuria. Photosensitization is a side effect that may accompany pheothiazine administration in ruminants (especially in calves) and fowls when animals are subsequently exposed to direct sunlight. Accumulation of unmetabolized phenothiazine sulfoxide (photodynamic agent) causes photosensitization keratitis manifested by ulceration of cornea and blindness. Skin may show sunburn like symptoms viz. reddening and thickening of ear and muzzle and development of scab.
**Contraindications:**

a) The drug may cause poisoning in cachectic, weak, anaemic, constipated and emaciated animals and therefore is strictly contraindicated in these animals.
b) Concurrent use of phenothiazine and organophosphates is contraindicated as phenothiazine potentiates organophosphate toxicity.
c) The drug is contraindicated in pregnancy (during the last month of gestation). The drug causes no interference with conception or embryonic development.

**Disadvantages:**

a) Pink coloration of milk due to the presence of drug metabolites (harmless) does not allow its commercial use for human consumption for 96 hours and therefore cannot be used in lactating animals.
b) The red coloring of urine causes permanent discoloration of hair and wool of animals resulting in economic losses, especially to the sheep farmers.
c) There is evidence of drug resistance against some strains of *Haemonchus* to phenothiazine when used for longer periods.

**b. Benzimidazoles**

These have broad spectrum of anthelmintic activity, high degree of efficacy, good margin of safety and have versatility of administration. The first benzimidazole introduced in 1960, was thiabendazole (TBZ).The structure of TBZ was modified with an aim to develop related drugs with more desirable anthelmintic properties. The imidazoles possess antibacterial, anthelmintic, antiprotozoal and antifungal actions.
**Chemistry:** All bezimidazoles have same central nucleus i.e. 1,2- diaminobenzene.

**Mode of action:** All the benzimidazoles act on parasites by interfering with their energy generating metabolism:

a) All benzimidazoles except mebendazole and flubendazole, are inhibitors of fumerate reductase enzyme system and thereby inhibit the generation of mitochondrial ATP. In the absence of usable energy, the parasite dies.
b) Mebendazole and flubendazole primarily act by inhibiting glucose transport. They bind to free beta-tubulin, inhibiting its polymerization and thus interfering with microtubule–dependent glucose uptake. In absence of glucose there is depletion of the worm's glycogen reserve, which renders its unable to produce ATP necessary for survival. But these two do not inhibit fumerate reductase system.
c) The primary site of action of cambendazole and fenbendazole is fumerate reductase inhibition. In addition, like mebendazole and flubendazole they also inhibit glucose transport. This explains their effecteness against certain parasites that lack fumerate reductase system.
d) Thiabendazole also inhibits egg production by helminths by inhibiting protein synthesis.

**Thiabendazole (R & LF):** It is rapidly absorbed and rapidly eliminated within 48 hours. Its **zero-day withdrawl period** ensures its popularity with farmers. It may also be used in **lactating cows** producing milk for human consumption. Dosages: Oral: Cattle: 100 mg/kg; sheep: 50-75 mg/kg; Horse: 50 mg/kg; Poultry: 1000 mg/kg.

**Other Benzimidazoles:**

**Albendazole (R, T, LF)**: The drug is metabolized to the sulphones and sulfoxide which may provide the liver fluke and tapeworm activity. Drug residue persists for several days. Withdrawal period for slaughter of cattle and sheep is 10-14 days and lactating cows should not be treated with albenazole. High doses may be embryotoxic and teratogenic.
Dosages: Oral: Cattle and sheep: 7.5 mg/kg (15mg/kg for adult liver fluke); Swine: 5 – 10 mg/kg.
**Cambendazole (R, T)**: Mainly used to treat pig and avian roundworms, fairly toxic, embryotoxic and teratogenic.
Dosages: Oral: Cattle, Horse, sheep and Swine: 20 mg/kg.
**Fenbendazole (R, T, LF)**: No embryotoxicity.
Dosages: Oral: Cattle: 7.5 mg/kg; Horse, Sheep, Goat and Swine: 5 mg/kg; Dog and cat: 50 mgx 3 days. For Ascarids in horses and swine and *Moniezia* in ruminants @ 10 mg/kg.
**Parbendazole (R )**: Effective against GI nematodes and lungworms. Embryotoxic and teratogenic.
Dosages: Oral: Cattle, Sheep and Swine: 20-30 mg/kg.
**Flubendazole (R)**: Mainly used to treat pig roundworms. No embryotoxicity.
Dosages: Oral: Pigs: 5mg/kg or 30 ppm in feed; Sheep: 10 mg/kg.
**Mebendazole (R, T)**: Effective against roundworms, tape worms (including larvae). It has some antifilarial activity. No embryotoxicity.
Dosages: Oral: Sheep and Horse: 10 mg/kg; Pig: 30 ppm in feed for 10 days; Dog and cat: 25-50 mg/kg twice daily for 5 days; Poultry 10 mg/kg for 3 days.
**Oxfendazole (R, T, FL)**: Oxfendazole is the sulfoxide metabolite of fenbendazole and responsible for the activity of both these anthelmintics.
Dosages: Oral: Cattle, Sheep and Swine: 4.5-5mg/kg; Horse: 10 mg/kg.
**Oxibendazole (R)**: Usually employed as horse anthelmintic. High doses are embryotoxic.
Dosage: Oral: Horse: 10 mg/kg; Pig: 10-15 mg/kg; Cattle: 5-10 mg/kg; Sheep: 5 mg/kg.
**Luxabendazole (R, FL)**: No teratogenic or mutagenic effects. Mainly used in sheep.
Dosage: Oral: 7.5 mg/kg (10 mg/kg for flukes).
**Triclabendazole (FL)**: It is an **antitrematodal** drug (see antitrematodal drugs).

**Benzimidazole Pro-Drugs**

These compounds are metabolied *in vivo* to produce benzimidazoles and need to be administered at doses high enough to produce sufficient active metabolites. Their mode of action, pharmacokinetics and spectrum of activity are similar to those of benzimidazoles. These drugs are:
**Febantel (R)**: It is a precursor of fenbendazole. Effective against GI nematodes.
Dosage: Oral: Cattle: 7.5 mg/kg; Sheep & pigs: 5 mg/kg.
**Netobimin (R,T,FL)**: It is a pro drug of albendazole. Effective against GI nematodes, their larvae, tapeworms and flukes. Teratogenic.
Dosage: Oral or Injection: Cattle: 7.5 mg/kg; Sheep: 7.5 mg/kg for roundworms and 20 mg/kg for inhibited larvae, flukes and tapeworms.
**Thiophanate (R)**: It produces the metabolite lobendazole. Active against most nematodes of farm animals.
Dosage: Oral: Cattle, sheep, goat and swine: 50-100mg/kg.

**Pharmacokinetics of Benzimidazoles**: Except thiabendazole, albendazole and oxfendazole, only limited amounts of a dose of any of the benzimidazoles are absorbed from the GI tract of the host as they are poorly soluble in water.
**Administration**: Benzimidazoles are administered only orally as drench, or as powder or granules in feed.

**Contradications**:

a) Because of tissue and milk residues a sufficient withdrawal period for slaughter of meat animal is required and the milk of the treated animals should not be used for human consumption.
b) Parbendazole, cambendazole and albendazole produce a teratogenic effect when given to pregnant ewes in early pregnancy (first 45 days) and therefore these types of drugs are contraindicated during early pregnancy in sheep and cattle. Mebendazole, fenbendazole, oxfendazole, flubendazole, luxa bendazole and thiophanate are free from teratogenic effects.

**Safety and toxicity**: The benzimidazoles are extremely well tolerated by domestic and wild animals in general at therapeutic doses and they can be given without side effects to even young, weak and debilitated animals. But some of the benzimidazoles produce teratogenic effect during early pregnancy.

**c. Imidazothiazoles**

**Butamisole Hydrochloride**: It is an injectable anthelmintic used in dogs to treat whip worm (*Trichuris vulpis*) and hookworm (*Ancylostoma caninum*) infections. It has low margin of safety. Toxic symptoms include vomiting, ataxia, recumbency and convulsions.

Dose: A single SC injection @ 2.4 mg/kg.

Contraindications:

a) In severely diseased or debilitated animals, animals with renal and hepatic disorders.
b) In heartworm positive dogs as it may cause fatality (the cause of death is not fully known).

**Tetramisole and Levamisole**:

Levamisole was developed following the introduction of tetramisole in 1966.Tetramisole is a racemic mixture of two isomers and the anthelmintic activity of mixture rested almost solely with the l-isomer, levamisole.This discovery made tetramisole an obsolete drug. By using levamisole the dose could be reduced to half, which provided both a more economic formulation and an increase in safety margin.

**Chemistry**: Levamisole is the levo-isomer of dl-tetramisole. It is used as hydrochloride salt, which is highly soluble in water and therefore can be given orally or by injection.

**Anthelmintic activity**: Levamisole is a commonly used antinematodal drug because of its broad range of activity in a large number of hosts (sheep, cattle, pig, horse, chicken, dog and cat). It is effective against almost all GI nematodes, lungworms and hookworms in ruminants, canine, horse, pig and chicken. Larval and immature stages of GI parasites of ruminants are effectively removed by levamisole. In poultry it is effective against *Capillaria obstignata*, *Ascaridia galli* and *H.gallinarum*. But it has no activity against flukes, tapeworms and protozoa.

**Mode of action**:

a) The drug affects the neuromuscular system of the parasite by acting as cholinergic agonist. It has a nicotine-like action, stimulating and subsequently blocking the neuromuscular junctions. The result is sustained muscle contraction and paralysis of nematodes. It also acts as a ganglionic stimulant causing muscular paralysis. Most nematodes are passed in the feces within 24 hours.
b) At high concentration in parasites, levamisole, like benzimidazoles interfere with carbohydrate metabolism by inhibiting fumerate reductase enzyme system.

**Effect on host immune system**: Levamisole modulates immunity of the host through stimulation of cell mediated immune reactivity by enhancing the rate of T-lymphocyte differentiation and proliferation, responsiveness to antigens and mitogens and activity of effector lymphocytes. It is highly beneficial in immunologically depressed animals.

**Pharmacokinetics**: Levamisole is rapidly absorbed and carried to all parts of the body. Mainly excreted through feces and urine, and in small amounts also through exspired gases. Tissue residues of the drug are not appreciable.

**Dosage and Administration**: Administered as bolus, soluble drench and wettable powder for addition to drinking water, SC injectable solution and dermal spot-on.
**Levamisole**: Oral: Cattle, sheep, goat and pig: 7.5 mg/kg in a single dose; Poultry: 25-50mg/kg SC injection: 7.5 mg/kg (@ 2 ml per 50 kg of 18.2% solution); As pour-on: 10mg/kg. As an immunostimulant: @ 2.5mg/kg oral or SC.
**Tetramisole**: Oral or SC: Cattle, sheep, goat and pig: 15 mg/kg in a single dose (total dose should not exceed 4.5 gm for cattle).

**Safety and toxicity**: Compared to benzimidazoles tetramisole and levamisole have a narrow margin of safety. Levamisole is well tolerated at recommended dose level. Cattle treated orally should not be slaughtered within 48 hr (for oral) and 7 days (for injection) of treatment. The drug should not be given to dairy animals producing milk for human consumption.

**d. Tetrahydropyrimidines**
**Pyrantel**: An imidazothiazole derivative. It is used as tartrate or palmoate salts.
**Effectiveness**: Broad-spectrum drug against GI parasites of sheep, cattle, swine, horse and dogs.
**Mode of action**: Affects neuromuscular system of the parasite in the same way as levamisole by acting as a cholinergic agonist. The drug causes depolarizing neuromuscular blockade resulting in sustained muscle contraction and paralysis of nematodes.
**Pharmacokinetics**: Pyrantel tartrate is well absorbed from the GI tract of pigs and dogs but absorption less in ruminants. The drug is quickly metabolized in the body and excreted in urine and feces. The palmoate salt is poorly soluble in water, so less absorbed in the gut allowing the drug to reach pinworms and be effective against them in the lower end of large intestine. So it is effective in the treatment of pinworm infection of lower digestive tract in dogs.
**Administration and Dosage**: Orally as a drench in ruminants, by stomach tube in horses and in swine it is given in feed, in dogs as suspension or tablets.
Pyrantel tartrate (Banminth): Dosage: Horse: 12.5 mg/kg; Swine: 22 mg/kg (maximum 2gm/animal); Cattle, sheep and goat: 25 mg/kg.
Pyrantel palmotate (Pyraminth): Dosage: Horses: 6.6 mg base/kg; Dogs (>2.2 kg): 5mg base/kg; Dogs: (<2.2 kg): 15 mg/kg.
Pyrantel fumerate: Sheep: 12.5 mg/kg.
**Contraindications**: In severely debilitayted animals (due to nicotinic action). Because of its cholinergic property, it should not be administered together with other cholinergic drugs like levamisole (may lead to potentiation of toxicity).
**Morantel**: It is a methyl ester of pyrantel. Principallly morantel tartrate but also the fumerate salt is used as veterinary anthelmintic. The salts of morantel have greater anthelmintic activity than the pyrantel. Their pharmacological properties are similar. Morantel tartrate is a safer drug than pyrantel tartrate.
**Administration and dosage**: Morantel tartrate (Banminth II): Orally as aqueous solution: Dose: Sheep: 10 mg/kg; Cattle: 8.8 mg/kg. A 4% ointment of the tartrate salt is used to treat *Thelazia* eye infections of cattle.

**e. Organophosphorus (OP) Compounds**:
The OP compounds were originally developed as systemic insecticides. Subsequently they are found to have also some anthelmintic property, but their safety is often poor. The compounds used in farm animals are coumaphos, crufomate, haloxon and naphtholphos, and in horse, dog and cat are dichlorvos and trichlorphon.
**Mode of action**: The main effect of OP compounds on animal parasites is inhibition of acetyl cholinesterase (AChE) enzyme, leading to an interference with neuromuscular transmission and consequent paralysis of the parasite. AChE of host and parasites and of different species of parasites vary in susceptibility to OP compounds. The degree of safety of OP compounds for the host is probably related to lack of susceptibility of host AChE to the drug. It has been found that the AChE of host and the nematodes are not identical.

**Coumaphos (Asuntol)**: Originally developed as pesticide for treatment of external parasites of livestock and later used as an anthelmintic. The advantage of this drug is that it can be used in **lactating animals** without requiring the milk to be discarded after treatment. It is effective against *Haemonchus*, *Ostertagia*, *Trichostrongylus* and *Cooperia*. It is mainly used as a helminth preventive. The powder of the drug is given as a food supplement @ 2 mg/kg daily for 6 days or as single dose @ 15 mg/kg for cattle and 8 mg/kg for sheep. The drug has narrow margin of safety and only healthy animals are dosed.

**Dichlorvos**: It is effective against *Toxocara,Toxascaris*, *Ancylostoma*, *Unciaria*, *Oesophagostomum* spp., *Ascaris suis*, *Trichuris suis*, *Parascaris equorum*, small Strongyles, *Oxyuris equi*, and *Strongylus vulgaris*. It is therefore a **valuable anthelmintic for dogs, cats, pigs and horses**. A chief advantage of dichlorvos over many broad-spectrum anthelmintics in dogs and swine is its efficacy against whipworms. It is not effective against migrating hookworms and ascarid larvae and has no effect on tapeworms.
Dose: Dichlorvos phosphate pellets are administered in the feed. The single treatment doses are: Horses: 31-41 mg/kg in feed; Foals: gel formulation @ 20 mg/kg for bots and ascarids. Swine: 11-22 mg/kg; Dogs: 27-33 mg/kg; Puppies and Cat: 11 mg/kg.
**Haloxon**: It is closely related to coumaphos. It is effective against the GI nematodes of horse, sheep, cattle and pig. It is probably the safest OP anthelmintic in ruminants.
Dosage and Admiminstration: Orally in bolus, drench, or paste form.
Cattle: 44mg/kg; Sheep & Goat: 35-50 mg/kg.
Contraindications:

a) Haloxon, like other OP compounds should not be used simultaneously with other cholinesterase inhibiting agents or chemicals (carbontetrachloride).
b) Third stage of pregnancy in ewes and cows.
c) Lactating cows or goats producing milk for human consumption because of residues.
d) Withdrawal period of seven days prior to slaughter.

**Trichlorphon**: Trichlorphon is a prodrug, metabolises rapidly to dichlorvos which is responsible for its therapeutic action. It is used as an insecticide (Neguvon) as well as anthelmintic in animals, principally in horse. It is used for the treatment of Bots in horses, for GI nematodes in cattle, *Haemonchus contortus* and *Oestrus ovis* (nasal grab) in sheep and *Ascaris* in pigs.
Dose: Oral: Horse: 20-40 mg/kg for nematodes and bots; Dogs: 75 mg/kg for each of three treatments at 3-4 days intervals; Sheep: 55 mg/kg.

**Naphtholphos**: Is a medium spectrum OP compound used in sheep and cattle mainly against parasites of the abomasum and small intestine, but it is ineffective against the parasites of large intestine of ruminants.The drug has a very low margin of safety in chickens.
Administration and dosages: Orally as bolus, drench or feed additive; Cattle and sheep: 50 mg/kg.

**Crufomate**: Its oral administration provides anthelmintic activity in cattle and pour-on method of application control warble fly. The drug is highly effective against *Haemonchus, Cooperia, Bunostomum,* and *Ostertagia*, but less effective against *Trichostrongylus, Oesophagostomum, Capillaria* and lungworms.
Dosage: Cattle: Oral: 40 mg/kg, single dose.

**f. Macrocyclic lactones: Avermectins and Milbemycins**

**Avermectins**: Avermectins are a group of chemically related anthelmintics produced by the fermentation of actinomycete, *Streptomyces avermitilis*. There are eight different components of avermectins namely A1a, A2a, B1a, B2a and A1b, A2b, B1b and B2b. Each of these components has anthelmintic activity. The avermectins are also macrocyclic lactone derivatives, but in contrast to the macrolide or polyene antibiotics, they lack significant antibacterial or antifungal activity. The avermectins in commercial use are ivermectin, abamectin and doramectin.

**Ivermectin** is a mixture comprising 80% 22, 23 dihydroavermectin B1a and 20% 22, 23 dihydroavermectin B1b. It is a very potent nematocide and ectoparasiticide (endectocide) by oral and parenteral routes.
**Activity**: Ivermectin is effective against all stages of parasitic GI nematodes and lungworms including canine heartworm larvae. It is also a potent ectoparasicide and effective against warbles, lice and mites.It has no activity against tapeworms and flukes. Dung of ivermectin treated animals does not decompose (ecological threat).
**Mode of action**: The normal function of GABA in mammals and invertebrates, is inhibition of neurotransmission. Macrocyclic lactones/Avermectins cause paralysis of the worm by potentiation of GABAergic transmission (by opening chloride channel) between nerve and muscle. Potentiation of GABA leads to hyperpolarisation of postsynaptic cells and cosequent muscular paralysis. Flukes and tapeworms do not use GABA as a neurotransmitter and are not affected by avermectins. The lack of GABA related toxicity in man is explained by its low affinity for mammalian GABA receptors and its inability to penetrate the mammalian blood brain barrier. Recent evidence suggests that macrocyclic lactones act by binding to a glutamate gated chloride channel receptor in nematode and arthropod nerve cells. This results in opening of the channel (only in invertebrates) and influx of chloride ions leading to flaccid paralysis. Either such glutamate gated chloride channels are not involved in motor control of cestodes and trematodes or such glutamate gated chloride channel receptors are not present in cestodes or trematodes].
**Metabolism**: Ivermectin is readily absorbed, especially when given parenterally. High conc. of drugs sustained in tissues for long periods and residues occur mainly in the liver and fat. The drug is excreted in the feces (98%) and urine (2%).
**Dosage**: Cattle: 0.2mg/kg (Oral or SC); Sheep: 0.2 mg/kg orally; Horses: 0.2mg/kg (Oral); Swine: 0.3 mg/kg, SC; Dogs: 0.006-0.012 mg/kg as tablet orally or in food (monthly, as a preventive for heartworm) or 0.2 mg /kg, SC (2 injections at 14 days interval in mange infections).
**Toxicity**: The drug has minimum 10-fold margin of safety for ruminants, horses, swine and dogs. It should not be administered parenterally to horses and may be toxic to certain breeds of dogs (Idiosyncratic reaction in Collies). It is not embryotoxic in domestic animals, but is teratogenic to rodents.
Acute toxic signs are: CNS depression, listlessness, ataxia, recumbency followed by death.
**Precautions**:

a) Cattle must not be treated within 21 days of slaughter.
b) Ivermectin should not be used in milk producing animals or in dairy cows for 28 days prior to calving.

**Abamectin and Doramectin**: Pharmacological actions and dosages are same as ivermectin.

**Milbemycins**
**Milbemycin D**: It is a natural product of *Streptomyces hygroscopicus* sp. *Aureolacrimosus*, and only used for treating dogs. It is active orally against dog roundworms and prophylactic against heartworms at higher monthly doses.The mode of action is similar to ivermectin. Higher doses cause neurological disorder in Collie breeds of dogs.
Dose: 1mg/kg once monthly.
**Milbemycin oxime**: It is used is used as tablets orally in dogs at monthly intervals for prevention of heartworm disease and to treat hookworms.
Dose: 0.5mg/kg once monthly.
**Moxidectin**: It is a semisynthetic derivative of milbemycin used for treating cattle. It is administered SC in cattle and has same broad spectrum of activity against roundworms and ectoparasites as ivermectin.
Dose: 0.2 mg/kg SC.

**g. Drugs Acting Against Heartworms**
**Elimination of adult heartworms**:
**Thiacetarsamide sodium**: Chemically it is an arsenical compound and is the only drug used for the elimination of adult heartworms in dogs. The drug does not affect the circulating microfilariae.

**Mode of action**: The drug interferes with the energy production of the parasite by inhibition of glycolysis. The trivalent arsenic tends to bind sulfhydryl (-SH) groups, thereby altering the tertiary structure of proteins and the active site of enzymes in both parasite and host.

**Effectiveness**: Following four therapeutic doses of thiacetarsamide, adult worms die usually within 5-7 days and occasionally not until 14 days.The dead worms are swept out of the heart by the flowing blood and lodge in the pulmonary artery, especially in the diaphragmatic lobes, where phagocytosis of dead worms occur during the next 2-3 months. To avoid embolism, absolute rest during the first two weeks is necessary.

**Administration and Dosage**: Dogs: IV @ 2.2 mg/kg twice daily for 2 days.

**Precautions**:

a) The drug is hepatotoxic and nephrotoxic therefore proper functioning of liver and kidney must be attained before starting treatment.
b) The drug is highly irritating to subcutaneous tissues. So, during IV injection care must be taken to avoid perivascular leakage as it may result in local swelling and sloughing. Injection of steroids into the area helps in reducing inflammation.

**Toxicity**: The symptoms of arsenic toxicity like persistent vomiting, icterus or orange colored urine may be seen and the toxicity can be treated with dimercaprol @ 8.8mg/kg/day in 4 divided doses.

**Elimination of heartworm microfilariae**: Elimination of heartworm microfilariae is essential as they cause glomerular damage in kidney and the preventive drug, diethylcarbamazine is not safe for use in dogs until they are cleared of microfilariae.

**Dithiazanine iodide**: It is an intense blue-violet powder, poorly soluble in water. It is the only drug used as a heartworm microfilaricide in dogs.

**Mode of action**: The exact mechanism by which dithiazanine clears circulating microfilariae from the blood is not known. It is thought that the drug inhibits the glucose uptake by the parasite and consequently affects the ATP formation. The parasites lose their motility, become trapped in the capillary beds and are finally phagocytized by host cells.

**Administration and Dosages**: Available as either powder or tablet and is administration orally just after or during feeding: Dose: 6.6 mg/kg/day for 7-10 days as microfilariaecide.

**Precaution**: It should be given 6 months after the adulticidal drug. The interval allows improvement in physical condition of the dog following the stressful use of adulticidal thiacetarsamide.

**Toxicity**: Repeated dosing may produce vomiting, diarrhea, anorexia and asthenia.

**Preventive programme for heartworm disease in dogs: Two approaches are followed**:

A. The adulticidal drug is given at 6 months intervals @ 2.2 mg/kg IV twice daily for 2 days.
B. Using larvaecidal drugs that kill the infective 3rd stage or developing 4th stage larvae (Diethylcarbamazine (DEC), ivermectin or milbemycin D etc). Monthly treatment with ivermectin as compared with the requirement of daily dosing with DEC, gives the former drug the advantage as a potential preventive.

**Diethylcarbamazine citrate**: It is a piperazine derivative. DEC is used as a heartworm preventive. The drug also act against microfilariae but unfortunately sometimes a fatal shock type of reaction occurs if the drug is given to microfilariae positive dogs. So, an infected dog must be cleared of adult heartworms and microfilariae before starting it on DEC prophylaxis. In human it is used in filarial infection caused by *W. bancrofti* and tropical eosinophilia.

**Mode of action**: The most important action of DEC appears to opsonization of microfilarial membranes so that they are readily phagocytosed by tissue fixed monocytes, but not by circulating phagocytes. The drug also affects the nervous system of the parasites and causes paralysis of the worm. It may also interfere with the parasites arachidonate metabolism.

**Administration and Dosage**: The drug is rapidly absorbed from the GI tract and its rapid metabolism and excretion accounts for its low toxicity. It is administered in feed or just after feeding as tablet, syrup or powder each day throughout the mosquito season and 2 months following.

**Dosage**: Dog: @ 6.6 mg/kg/day.

**h. Miscellaneous Antinematodal Drugs**

**n-Butyl chloride**: It is a colorless liquid administered in gelatin capsules to dogs and cats after overnight fasting for control of ascarid and hookworm infections. It is non toxic to small animals.

Dose: Dog and Cat: body wt < 2.25 kg: 1 ml; 2.25-4.5 kg: 2 ml; 4.5-9 kg: 3 ml; 9-18 kg: 4 ml; > 18 kg: 5ml.

**Toluene**: It is a liquid coal tar hydrocarbon (methylbenzene), and used as anthelmintic against ascarid of hookworms of dogs and cats. In comparison to n-butyl chloride, it is more efficacious but more toxic. Combination of these two drugs is synergistic.

Dose: Oral: Dog, cat, puppy/kitten: As gelatin capsules @ 0.22ml/kg.

**Tetrachloroethylene**: It is a halogenated hydrocarbon, colorless, volatile liquid has been used mainly against hookworm infections of dogs, cats and humans and against GI nematodes of ruminants. Tetrachloroethylene has largely been replaced by other better drugs because of its several disadvantages and toxicity (dizziness, incoordination, liver damage and even death).

**Disadvantages**:

a) In ruminants, rumen reduces the activity of the drug. Therefore, bypassing of the rumen by stimulating closure of oesophageal groove is essential.
b) In small animals the animals must be kept on fat free diet for 48 hours prior dosing as fat increases the absorption of the drug from the gut and may precipitate toxicity.
c) Food and water should be withheld 12 hours before and 4 hours respectively after drug administration.

**Contraindications**:

a) In tapeworm infested animals as irritation of these worms may results in their balling up, occlusion and even rupture of gut.
b) Febrile, debilitated, nursing animals or weighing less than 1 kg.

**Dose**: Dog and Cat: Orally as gelatin capsules @ 0.22 ml/kg

**Bephenium hydroxynaphthoate:** A quaternary ammonium compound, bitter yellow powder, insoluble in water.

**Effectiveness**: Most effective against mature hookworms of dogs and cats and humans and also GI parasites of ruminants specially Nematodirus spp. and also *Tichostrongylus, Haemonchus, Ostertagia, Bunostomum , Oesophagostomum* and *Cooperia* species.

**Mode of action**: The drug affects the neuromuscular system of the parasite in the same way as levamisole by acting as a cholinergic agonist and causes depolarizing type neuromuscular blockade resulting in sustained muscle contraction and paralysis of nematodes.

**Administration and Dosage**: Cattle and Sheep: As a drench: @250mg/kg, single dose; Dogs: as tablets: 35 mg/kg in two divided doses. Overnight fasting and post treatment purgatives are not required.

**Precaution**: The drug produces gastric irritation, nausea and vomiting, hence an antiemetic should be given before medication.

**Toxicity**: Safe at therapeutic doses. Occasionally may cause vomiting and diarrhea.

**Thenium closylate**: It is a colorless crystalline solid, analog of bephenium. It is particularly effective against mature and immature hookworms but has poor action against Ascaris unless combined with piperazine. It may cause vomiting in dogs.

**Mode of Action**: Same as Bephenium.

**Administration and Dosage**: As tablet, or capsule or in feed (one-day treatment ). Fasting or purgation is not required.

Dogs: > 4.5 kg body wt.: 500 mg base as a single dose; Pups: < 4.5kg: 125 mg twice.

**Disophenol (Ancylol)**: Chemically it is 2,6-diiodo-4-nitrophenol. It is an injectable antihookworm compound used in dogs and cats.

**Mode of Action**: The drug affects the energy production of the parasites by inhibiting the oxidative phosphorylation in the mitochondria.

**Administration and Dosage**: Dogs & cats: single SC injection: 10 mg/kg (as 4.5% solution = 45 mg/ml).
**Advantages**: Can be used in very young animals and even in heavily parasitized animals without stress. No need of fasting.

**Hygromycin B**: This is an antibiotic obtained from *Streptomyces hygroscopicus* with anthelmintic activity.
**Effectiveness**: Highly effective against *A. sum* and also *Oesophagostomum* of swine and *A. galli*, *Capillaria obstignata* and *H.gallinarum* in chickens.
**Administration and Dosage**: added as powder to feed of swine and chickens for several weeks.
Dose: Swine: @ 13.2 g / 1000 kg of ration (given to weaned pigs up to 6 months of age i.e. during period of ascarid susceptibility), intermittently (8 weeks on and 8 weeks off) to avoid toxicity; Chickens: 8 gm/900 kg feed.
**Toxicity**: Continuous feeding of the antibiotic over 10 months may cause hearing loss and cataract in swine. No adverse effect in chickens or on egg production at the recommended dose level.

### 3. Anticestodal Drugs

These are the drugs effective against cestodes or tapeworms and are of two types:

i) **Taeniafuges:** These drugs simply cause expulsion of tapeworms. They generally paralyse the tapeworm and are combined with purgative to fecilitate expulsion e.g. older natural organic anticestodal drugs like arecoline.
ii) **Taenicides:** They cause actual death of the tapeworms in situ. e.g. synthetic organic compounds like bunamidine.

**Classification**: Anticestodal drugs are classified as:
a) Natural compounds b) Inorganic compounds and c) Synthetic organic coumpounds.

#### a. Natural (organic) Anticestodal Compounds:

**Earliest anticestodal compounds**: They were mostly plant origin and used for man and animals. They have been replaced by more efficacious and safer synthetic organic anticestodal drugs. Some of them are as follows:
**Pumkin seeds**: The minced pumkin seed has anticestodal activity and still used in some countries. The active principle is cucurbitine. It has low efficacy but high safety even in debilitated and young patients.
**Male fern**: **(Dryopteris felix mas)**: The powdered rhizome of this fern was best known and had been most commonly used by the Greek physicians against human cestodes. The active principle was found to be filicic acid that caused paralysis of the tapeworm.
**Kamala**: Source: Glands and hairs covering fruits of a plant *Mellotus philippinensis* found in Philippines, India, and China. Previously it was the drug of choice for cat tapeworms like *Dipylidium caninum* and *Taenia taeniformis*. Kamala causes paralysis of both cestodes and host intestinal muscle and never used in veterinary medicine.
**Nicotine**: Source is *Nicotiana tabacum*. It was commonly given with copper sulphate for removal of ruminant tapeworms and roundworms. The drug causes persistent depolarization of the neuromuscular junction followed by paralysis of the worm. The efficacy and safety of the drug are low.

**Arecoline**: It is an alkaloid obtained from seeds of betel nut palm, *Areca catechu*. It is still used in dogs. Arecholine itself is unstable so its stable salts are used.
**Arecoline hydrobromide**: it is a white, bitter, crystalline substance.
**Effectiveness**: Against all tapeworms of dogs (*Taenia*, *Dipylidium*) including *Echinococcus*.
**Mode of Action**: It has two folds action. Arecoline salts affect the neuromuscular system of the parasite probably by acting as a cholinergic agonist resulting in the paralysis and detachment of the worm from the intestinal mucosa. Its local cholinergic action also increases the peristalsitic movement of the intestine so that the detached worm is expelled by purgation. The drug causes only temporary paralysis of the worm. So if purgation does not occur within 2 hours of medication, a saline purgative is given to dogs to induce evacuation.

**Administration and Dosage**: Orally as enteric coated tablets after overnight fasting. Dose: Dogs: 1 mg/kg.
**Toxicity**: Vomition, colic and diarrhea. Antidote is atropine sulphate @ 0.044mg/kg.
The drug is contraindicated in cats; excessively increases the tracheo-bronchial secretion and thereby causes suffocation.
**Arecoline acetersol**: It is a white tasteless powder. It is administered orally as tablets. The drug is hydrolysed in stomach, releasing the active moiety, arecoline. The drug is used in dogs and cats as anticestodal against *Taenia* and *Dipylidium* and as a laxative. Mode of action is similar to arecoline hydrobromide.
Dose: Dogs and adult cat: 4.9 mg/kg; 2.6 mg/kg as laxative.
**Arecoline carboxyphenylstilbonate**: It is used in dogs as an anticestodal drug against *Taenia* and *Dipylidium*. Other pharmacological actions actions are similar to arecoline hydrobromide.
Dose: Dogs: Orally as tablets @ 10.3 mg/kg.

**b. Synthetic Organic Compounds**
**Bunamidine salts**: Two bunamidine salts are clinically used as anticestodal drugs, and both are taenicides.
**Bunamidine hydrochloride**: It is a white crystalline powder, has good activity against all tapeworms of dog and cat including *Echinococcus granulosus*.
**Mode of Action**: Bunamidine salts disrupt the tegument of the parasite resulting into reduced rate of glucose uptake and ultimate death of the parasite. The dead worms are digested in the host gut. The drug does not cause purgation.
**Dosage**: Administered orally as coated tablets. Dog and Cat: Single dose @ 25-50 mg/kg after 4 hr fasting.
**Safety**: The drug is safe in all stages of pregnancy.
**Toxicity**: Vomiting and diarrhea. This can be reduced by using hydroxynaphthoate salt.
The drug may cause sensitization of heart muscle to catecholamine and sudden death of animals.
**Bunamidine hydroxynaphthoate**: The drug is safely used against *Moniezia* sp. in sheep and goats even in pregnany.
Dosage: Administered orally as drench @ 25-50 mg/kg.

**Niclosamide**: Chemically it is 2',5-dichloro-4' nitrosalicylanilide, yellowish powder, insolubie in water.
**Activity**: It is widely used against the tapeworm infections (mainly for *Taenia*) of dog, cat and man but it has poor efficacy against *Echinococcus* and variable for *Dipylidium*. It is also used against *Moniezia* and *Thysaosoma* infections in ruminants and tapeworm infections in lab. animals, monkeys and reptiles .It has also activity against intestinal flukes such as *Paramphistomum* in ruminants.
**Mode of Action**: It is a taenicide. The anticestodal activity is produced by

a) Inhibition of glucose absorption by the worm.
b) Uncoupling of oxidative phosphorylation in the mitochondria resulting in blockade of Kreb's cycle and accumulation of lactic acid in the worm and interference with anaerobic generation of ATP by the worm. This results in death of tapeworm and its digestion in the gut.
c) The cestocidal action of the drug may be also related to the overstimulation of ATPase activity of the mitochondria.

**Pharmacokinetics**: Oral absorption is poor and this accounts for its low toxicity. The absorbed part is metabolized to inert amine (aminoniclosamide) and rapidly excreted in urine.
**Administration and dosage**: Dog and cat: Orally as tablets @ 100-150 mg/kg; Cattle: As drench @ 50 mg/kg; Sheep and Goat: As drench @ 100 mg/kg. Overnight fasting is required in all animas before dosing. Rabbit, Chicken and Monkey: @ 100 mg/kg; Reptiles: @ 165 mg/kg.
**Safety and Toxicity**: It has wide margin of safety. Safe at all stages of pregnancy and in debilitated animals. The drug has no contraindications. Because of these advantages, niclosamide is extensively used as a taenicide both in human and vety. medicine.

**Dichlorophen**: Chemically it is 2,2'-methylene bis (4-chlorophenol). It is a white powder, insoluble in water. Most of the pharmacological properties viz. mode of action, kinetics, safety and toxicity are similar to niclosamide.
**Efficacy**: It is mainly used as a narrow spectrum taenicide in veterinary medicine. It is effective against *Taenia* and *Dipylidium* in dogs and cats. But it is ineffective against *Echinococcus*, thus it is not the drug of choice for this tapeworm. It has limited efficacy against *Moniezia* in sheep. In addition, the drug has bactericidal and fungicidal properties.
**Administration and Dosage**: Orally as tablets or suspension after overnight fasting. Pugative is not required. Dog, Cat and Sheep: 200 mg/kg

**Hexachlorophene**: It is mainly used as an antitrematodal drug for the treatment of liver fluke infection in sheep and cattle (for details, see antitrematodal drugs). The main anticestodal use of this drug is for the control of chicken tapeworms, especially of *Raillietina cesticillus*. The drug is toxic to dogs.
**Mode of Action**: Uncoupling of oxidative phosphorylation in the mitochondria and interference with anaerobic generation of ATP by the worm. This results in death of tapeworm and its digestion in the gut.
**Dose**: Chickens: Single dose @ 30-60 mg/kg after overnight fasting. The drug is combined with phenothiazine in poultry for removal of tapeworms and *Ascaris* simultaneously.

**Resorantel**: Chemically it is a hydroxynilide. It is an anticestodal for ruminants.
**Effiacy**: It is highly effective against *Moniezia* in both sheep and cattle and against *Thysaniezia gardi* in sheep. In addition, it has 90% efficacy in sheep and cattle against adult and immature rumen flukes (*Paramphictomum* spp).
**Mode of Action**: Same as hexachlorophene
**Pharmacokinetics**: The drug is rapidly excreted within 48 hours of treatment.
**Dose**: Sheep and Cattle: Administration as drench @ 65 mg/kg.

**Bithionol**: It is 2, 2'-thiobis (4, 6-dichlorophenol), white crystalline solid, insoluble in water. It has anthelmintic as well as bacteriostatic and antifungal activities.
**Indications and Effectiveness**: It is used for the treatment of tapeworm infections (especially *Taenia*) in dogs, cats and poultry. The drug is also used for the treatment of tapeworm (*Moniezia* and *Thysanosoma*) and rumen fluke (adult and immature *Paramphistomum*) infections of sheep, cattle and goats. The drug is also effective against lung flukes (*Paragonimus* spp) in dogs and cats.
**Mode of Action**: Same as hexachlorophene
**Pharmacokinetics**: Absorption from host gut is poor; excreted in bile; produces purgation due to its cholinergic effect on host gut.
**Safety and Toxicity**: Well tolerated by cats, dogs, cattle, sheep, goats and chickens. But sometimes emesis is seen in dogs and diarrhea is seen in all species.
Dose: Dogs, cats, sheep and goats: Oral: @ 200mg/kg as tablets, gelatin capsules or boluses; Chickens: 200 mg/kg, 2 doses, 4 days apart, in feed.

**Bithionol sulphoxide**: A derivative of bithionol. The special advantage of this drug is that it has equal anticestodal efficacy to bithionol in dogs, sheep at lower therapeutic dose level of 60 mg/kg and has excellent efficacy against liver flukes of both sheep and cattle.

**Uredophos**: An OP compound, introduced as broad spectrum anthelmintic for use against both nematode (*Ascaris* and hookworms) and cestodes of dogs and cats at the dose rate of 50 mg/kg. The most important feature of the drug is that it is 100% efficacy against *Dipylidium caninum* that is resistant to most other anticestodal drugs except praziquantel.
**Mode of Action**: Anticholiesterase agent.
**Toxicity**: Because of severe adverse reactions and even death the drug has been banned for clinical use.

**Nitroscanate**: It is active against tapeworms and roundworms of dogs but not suitable for cat.
Dose: Dogs: 50 mg/kg. It is very safe and can be given to **pups and pregnant and lactating bitches**.
Side effect: Vomiting.

**Praziquantel**: Chemically it is an isoquinoline and colorless, crystalline and bitter compound.
**Effectiveness**: It is a new broad spectrum anthelmintic effective against all species of Schistosomes pathogenic to humans and has unique, extremely high activity against wide range of adult and larval cestodes of both animals and man (including *Cysticercosis*). It is also effective against ruminant, poultry and snake tapeworms and certain flukes. But it has no activity against nematodes.
**Mode of Action**: The drug is quickly taken up by the susceptible worms and act by increasing the permeability of the nematode cell membrane to $Ca^{++}$. This causes the leakage of intracellular calcium from the membranes resulting in contraction of musculature and eventual paralysis and death of the worm. Praziquantel also modifies the parasite so that it becomes susceptible to host's normal immune responses.
**Pharmacokinetics**: Orally the drug is quickly and completely absorbed and has ubiquitous distribution (asset for its activity against adult and larval form of parasite at different locations like brain, musculature etc) and quickly inactivated in liver.
**Administration and Dosage**: Administered orally or IM. Dog and cat: @ 5 mg/kg, by either roué for all tapeworms; Sheep, Goats and Poultry: 10-15 mg/kg by either routé for all tapeworms; Snake tapeworms: 3.5-7 mg/kg.
For lungfluke infection (*Paragonimus* spp): Dog: 25 mg/kg /day for three consecutive days.
Human: Oral: @ 10-25 mg/kg for tapeworms; For Schistosomiasis and other flukes: @ 40 - 75 mg/kg.
For neurocysticercosis: @ 50 mg/kg in three divided doses for15 days (alternative is albendazole).
**Safety and Toxicity**: Drug has wide margin of safety. No teratogenicity or embryotoxicity orally.

**Benzimidazoles**: The cestocidal benzimidazoles are:
Mebendazole: Taeniasis in Dog and Cat: @ 22 mg/kg/day for 5 days; For adult *Echinococcus granulosus*: @ 160 mg/kg. For *Moniezia* in ruminants: @ 20 mg/kg.
Fenbendazole: Taeniasis in Dog and Cat: @ 50mg/kg/day for 3 days.
All the above are ineffective against *D. caninum.*
Oxfendazole, Cambendazole and Albendazole: For *Moniezia* in ruminants: @ 7.5-15 mg/kg.

**Anticestodal drugs for Horses**: The following drugs are found to be effective and safe against equine papeworms (*Anoplocephala* spp)
Mebendazole: @ 20 mg/kg; Niclosamide: @ 88 mg/kg ; Dichlorophen: 20 mg/kg
Bithinol: 7 mg/kg; Pyrantel palmoate: @ 13.2 mg/kg.

**c. Inorganic Compounds**
**Tin compounds: Metallic tin with its oxide (stannous oxide) or chloride of di-n- butyl tin dilaurate**: They are very much effective against tapeworms such as *T. solium, T. saginata* and *Dipylidium* in dogs; *Davinea* in poultry and were extensively used as anticestodal in man and domestic animals.
**Mode of Action**: Tin particles form a thin layer of coating on the cuticle of the tapeworm and rendering the strobila susceptible to digestion.
**Disadvantage**: Needs daily administration for several days and produces side effects and toxic effects. So advent of more efficacious and less toxic taenicides has limited their use.

**Lead arsenate**: It is highly effective against *Moniezia* and was in use worldwide for the treatment of *Moniezia* infection in lambs, calves and kids. It has low margin of safety and it should never be used in poultry.
**Mode of Action**: The drug is hydrolysed in the gut to lead and arsenic. The lead is transformed to lead oxide and the pentavalent arsenic to more toxic trivalent arsenic.

**Dose**: Administered orally as capsules without fasting. Calves > 3 months and Lambs > 2 months: 1 gm/ animal, single dose (Lambs < 2 months should not be treated); Calves < 3 months and kids: 0.5 g/animal, single dose.

## 4. Antitrematodal Drugs

These are the drugs effective against trematodes or flukes. Fascioliosis caused by *F. hepatica* is most common worldwide and has greatest economic importance. The rumen fluke, *Paramphistomum* in cattle and lung fluke, *Paragonimus* in dogs and cats are important.

### a. Drugs Against Adult Flukes:

**Carbon tetrachloride ($CCl_4$)**: It is a volatile colorless liquid, insoluble in water.

**Efficacy**: Effective against adult *F. hepatica*, well tolerated in sheep and economic. Thus it is mainly used in sheep in the treatment of fascioliosis. Earlier it was used for ascariasis in dog, cat and poultry; *Ancylostoma* of dog and cats and stomach worms of cattle, but has now replaced by more effective antinematodal drugs.

**Mode of Action**: The anthelmintic action of $CCl_4$ is thought to be indirect, through its metabolites or by inducing formation of toxic methylsterol in the host liver due to interference with the cholesterol biosynthesis. In the host, methylsterol is an itermediate metabolite in biosynthesis of cholesterol. $CCl_4$ blocks the cholesterol biosynthesis at a point that results in the formation and accumulation of toxic methylsterols in the liver, bile and urine of treated animals. This methylsterol is highly toxic to the flukes and produces lethal effects by interfering with the secretory and enzymatic activity of the gut epithelium of the parasite. Recently it has been known that it uncouples oxidative phosphorylation in the mitochondria and interferes with anaerobic generation of ATP by the flukes. This results in death of the flukes.

**Pharmacokinetics**: After oral administration $CCl_4$ is absorbed in the intestine (increased by fats and oil), metabolized in liver and the active metabolite is excreted in bile and urine. So the adult flukes (12 weeks or older) living in the bile ducts are killed but the immature flukes living in the liver parenchyma are not affected.

**Administration and Dosage**: Sheep: Orally: @1-3 ml as capsules or as drench with 300-600 ml of liquid paraffin, in morning before feeding; IM or SC @ 4 ml in liquid paraffin containing butyl alcohol (local anaesthetic); Cattle: IM or SC @ 30 ml (or 1ml/9 kg) in liquid paraffin containing butyl alcohol (local anaesthetic); Dogs: 1-5 ml orally (0.1-0.2 ml/kg) in gelatin capsules; Poultry: 1-5 ml orally.

**Toxicity and Disadvantages**:

a) Lacks activity against immature flukes.
b) Highly toxic to mammalian liver (hepatotoxic). So cannot be used in cattle, horse, pig and cat.
c) High dose causes giddiness, unconsciousness and cardiovascular collapse.
d) Toxicity is more in debilitated animals, animals with diseased liver, high fat diet, in cold weather (due to decrease excretion through expired air).

**Hexachloroethane**: It is a chlorinated hydrocarbon, white crystalline substance.

**Effectiveness**: Highly effective against all species of adult *Fasciola* in cattle and also against *Haemonchus* and *Trichostrongylus*. But it is not effective against immature flukes and intestinal nematodes of ruminants.

Mode of Action: Act by uncoupling oxidative phosphorylation in the mitochondria and interferes with anaerobic generation of ATP by the flukes. This results in death of the flukes.

**Administration and Dosage**: Orally: Sheep: 8-15 gm/ animal; Cattle: @ 10 gm/50 kg (Pretreatment at monthly interval during snail season).

**Toxicity**: Hepatotoxic but lesser than $CCl_4$, so used as alternative in cattle against *Fasciola* infections.

**Limitations**: Hepatotoxicity, frequent side effects and dietary precautions in sheep and cattle compelled replacement of the drug by newer drugs.

**Hexachloroparaxylene**: Chemically it is chlorinated derivative of benzene (1,4-bis-trichloromethyl benzene).

**Effectiveness**: It is a highly effective fasciolicide against *F. hepatica* in sheep. It is combined with phenothiazine for the treatment of liver flukes and GI nematodes in ruminants.
**Administration and Dosage**: Oral: Sheep: 150mg/kg; Cattle: 125mg/kg.
**Advantage**: It is superior to $CCl_4$ and hexachloroethane because: i. High tolerance in sheep and ii. Does not cause blood dyscrasia.

**Tetrachlorodifluoroetane**: It is a halogenated hydrocarbon, effective against only adult *F.hepatica* (not against immature forms) infection and well tolerated in sheep. Dose: Sheep: Oral: @300 mg/kg.
Disadvantage: The drug is not used in cattle since it is less effective against liver flukes and also produces severe toxic reactions.

**Hexachlorophene (Distodin)**: Chemically it is 2,2'- methylenebis ( 3,4,6- trichlorophenol).
**Efficacy**: It is used in the treatment of mature liver fluke infections in human and ruminants and cestode infections in canines. The drug is 100% effective against adult *F. hepatica* and *F. gigantica* in sheep and cattle. This is because the drug remains in free form in bile and the host metabolite (glucuronide) excreted in bile has high activity especially against adult flukes, as they remain in the bile ducts. However, the immature flukes (< 8 weeks old) bathed in the blood of liver parenchyma, are not affected because the free drug is less available to this immature flukes due to its plasma protein binding.
**Mode of Action**: Same as hexachloroethane
**Administration and Dosage**: Sheep and Cattle: Oral: @ 25 mg/kg
**Safety and Toxicity**: Less safe. Overdosing causes CNS symptoms, blindness followed by even death.

**Bithinol sulfoxide**:
**Activity**: Besides anticestodal properties, bithinol and its sulfoxide has excellent effecacy against rumen and liver flukes (*Fasciola hepatica, F. gigantica, Fascioloides magna* and *Paraphistomum* spp) of domesticated and wild ruminants. This drug is also much more effective against adult than immature flukes.
**Mode of Action**: Same as hexachloroethane.
**Administration and Dosage**: Sheep, Goat and Cattle: Oral: Administered as bolus or in feed @ 60 mg/kg.
Drug combination: i) Bithionol sulfoxide (@ 30mg/kg) + Hexachlorophene (@ 5 mg/kg): 100% effective against mature *F.hepatica* in cattle and sheep.
**Bromosalans**: This is the mixture of dibromosalans and tribromosalans. The drug has equal efficacy for adult flukes as other fasciolicidal drugs and has been used for the treatment of *F.hepatica* infection. An extra advantage of bromosalans is that it is 100% effective against juvenile flukes (6-10 weeks age).
Mode of Action: Same as hexachloroethane.
Dose: Sheep: Orally: 30 mg/kg (for adult flukes); 60 mg/kg (for juvenile flukes)
Safety: It has narrow therapeutic index of 3 in sheep.

**Oxyclozanide**: It is a salicylanilide compound having fasciolicidal activity. *In vivo*, it is only active against adult liver flukes that live in the bile duct. Like hexachlorophene and nitroxinyl, it is also not effective against immature flukes because of protein binding in blood.
**Mode of Action**: Same as hexachloroethane.
Dose: Oral: Cattle and Sheep: @ 15 mg/kg.
**Advantages**:

a) The drug is equally effective as $CCl_4$, hexachloroethane and hexachlorophene and is less toxic.
b) Drug has **zero withdrawal for milk** and short withdrawal period for slaughter.
c) It **can be given in therapeutic doses to debilitated and pregnant animals** without any side effects.

**Clioxanide**: Chemically it is 4'-chloro-3,5- diiodobenzanilide acetate. It is highly effective against adult and immature *F.hepatica* in sheep but the doses needed for immature flukes are less safe.
Dose: Orally for adult flukes: @ 15 mg/kg.

**Niclofolan**: It is an analogue of hexachlorophene. It is effective against adult F.hepatica in sheep, cattle and pigs at safe doses. It is also effective against immature flukes at higher doses but is less safe. The drug is mostly used in sheep.
**Mode of Action**: Same as hexachloroethane.
Administration and Dose: Oral: For adult flukes: Sheep: @ 2.7 mg/kg; Cattle: 3mg/kg; Parenteral: Sheep and Cattle: SC @ 0.6-1 mg/kg.
Precaution: Niclofolan is excreted in milk. Milk should not be consumed for 4-5days of post treatment.

**Nitroxynil**: Chemically it is 4-hydroxy-3-iodo-5-nitrobenzonitrile. It is an injectable fasciolicide, effective against adult liver flukes (*F.hepatica* and *F. gigantica*) in cattle and sheep, with some activity against fly larvae (*Oesterous ovis*) and blood sucking nematodes. It is also used to treat gapeworms (*Syngamus*) in poultry.
**Mode of Action**: Same as hexachloroethane.
**Administration and Dosage**: SC route. Since, when given orally, reduction of nitro group by microorganisms in rumen causes loss of anthelmintic activity.
**Dose**: Sheep and Cattle: SC @10 mg/kg; Poultry: 150-400 ppm in water.
**Precaution**: The drug is slowly excreted. So, withdrawal period for slaughter is 31 days and should not be used in cows producing milk for human consumption.
**Advantage**: Easy to administer SC than other fasciolicides that are given orally.
Safety: Margin of safety is only 4.

**Rafoxanide**: Chemically it is a halogenated salicylanilide.
**Activity**: Effective against adult and young (6-10 weeks old) liver flukes in sheep. It is also indicated in the treatment of blood sucking nematode infections (haemonchosis, bunostomiasis) and for tissue invading fly maggots (sheep nasal bot).
**Mode of Action**: Same as hexachloroethane.
**Dose**: Sheep: @ 7.5 mg/kg orally; Cattle: @7.5 mg/kg orally or @ 3mg/kg SC.
Pharmacokinetics: The drug is well absorbed, but slowly eliminated. So the drug cannot be used in lactating cows and requires 28 days withdrawal period for meat.

**Bromophenophos**: It is an organophosphoric acid ester, used for the treatment of mature *F.hepatica* infections in cattle. It has also good efficacy against immature liver flukes.
Mode of Action: Same as hexachloroethane.
Dose: Cattle orally @ 12 mg/kg.
Toxicity: Safety index is 3.
The toxicity of niclofolan, nitroxynil and bromophenophos is due to uncoupling of oxidative phosphorylation in the host also.

**Clorsulon**: Chemically it is benzene sulfonamide. It is an oral fasciolicide.
**Activity**: It is active against adult and young immature liver flukes (6-8 weeks old).
**Mode of Action**: The drug inhibits the glycolysis by inhibiting the glycolytic enzymes, 3-phosphoglycerate kinase and phosphogleromutase of *F.hepatica*. This enzymatic inhibition causes blockade of the Embden-Myerhof glycolytic pathway in the parasite and deprives the fluke of essential metabolic energy. This ultimately leads to death of the fiuke.
**Dose**: Cattle and Sheep: @ 7 mg/kg orally as drench or @ 4 mg/kg SC.
Safety: Safe for using in breeding and pregnant animals.

**Closantel**: Closantel has a broad range of anthelmintic activity, affecting both endoparasites as well as ectoparasites (endectocide) of animals. The drug is effective against adult and juvenile (6-10 weeks old) liver flukes, blood sucking nematodes, parasitic larvae of flies and to some extent against tapeworms, mange, mites and ticks.

**Mode of Action**: Same as hexachloroethane.
**Pharmacokinetics**: It is well absorbed both orally and SC.
**Administration and Dosage**: Orally or SC.
Dose: Sheep and Cattle: @ 5mg/kg SC or @ 10 mg/kg orally.
**Safety and Toxicity**: It has therapeutic index of 6. It is not carcinogenic, teratogenic or embryotoxic.

**Benzimidazoles**:
**Albendazole**: Highly effective against adult *F. hepatica* and *Fascioloides magna* in sheep and cattle and used therapeutically.
Dose: Oral: Single dose: Cattle: 10 mg/kg; Sheep: 7.5 mg/kg.
For Dicrocoelium infection in sheep (Single oral dose): Cambendazole: @ 50-100 mg/kg ; Thiabendazole: @ 200 mg/kg; fenbendazole: @ 100 mg/kg.

**b. Drugs Against Immature Flukes**
**Diamfenetide**: Chemically it is β,β'-bis ( 4-acetamidophenyloxy) ethyl ether.
**Activity**: In contrast to other fasciolicides, which are less active against immature flukes, diamfenetide has exceptionally high activity against the immature stages of liver flukes especially in sheep and comparatively less activity against adult flukes. It is inactive in cattle.
**Mode of Action**: The drug undergoes de-acylation in the liver of the host by hepatic enzymes (deacylase) and a high conc. of an active amine metabolite is formed in the hepatic parenchyma which is responsible for its activity. This amine metabolite causes rapid killing of immature flukes that are also located in the liver parenchyma until they are seven weeks of age. The flukicidal effect is due to affecting permeability of cells and vacuolation of tegument.
The amine metabolite is also rapidly inactivated by liver. Therefore, the drug is less effective against adult flukes as only a small amount of the active drug reaches to the mature flukes, located in the bile ducts.
**Use**: For prophylaxis of liver fluke disease in sheep and for the treatment of acute fascioliosis (due to immature *F.hepatica* in liver parenchyma) in sheep.
**Administration and Dosage**:
Curative: Sheep: Orally as suspension: @ 100 mg/kg, single dose. Subsequent use of an adulticidal drug is useful.
**Prophylaxis**: Combination of rafoxanide (effective against four weeks old to adult flukes) and diamfenetide (effective against day old to 10 weeks flukes) forms an ideal fasciolicide and is best for chemoprophylaxis of facioliosis.
**Precaution**: The drug should not be given to sheep producing milk for human consumption. It has a 7–day withdrawal period for meat.
**Safety**: Safe at recommended dose.

**c. Drugs Against Both Mature and Immature Flukes**
The only drug available is the triclabendazole.
**Triclabendazole**: Has a quite different spectrum of activity directed against liver flukes. It is highly potent against liver fluke *F.hepatica* from day old to adult. But it has no antinematodal activity.
Mode of Action: Not known. But it is thought to be different from that of other benzimidazoles.
**Pharmacokinetics**: The major metabolites of triclabendazole are corresponding sulphoxide and sulphone and the former is the major metabolite excreted in bile.
**Administration and Dosage**: Oral: Sheep and Goats @ 10 mg/kg; Cattle: @ 12 mg/kg.
Toxicity & Safety: The drug is well tolerated orally in sheep and cattle. It is neither teratogenic nor embryotoxic in rats.
**Precaution**: The drug should not be given to animals producing milk for human consumption. It has a 28–day withdrawal period for meat.

### d. Drugs Used in Paramphistomiasis

The following drugs are used effectively in the treatment of paramphistomiasis in sheep and cattle.
Niclosamide: @ 90 mg/kg, oral
Resorantel: @ 65 mg/kg, oral
Bithionol: @ 70 mg/kg, 2 doses orally at 48 hours interval.
Bithionol sulfoxide: @ 60 mg/kg, single dose.

### e. Drugs Used in Paragonimiasis

The drugs available for treatment of paragonimiasis in dog and cat:
Praziquantel: Drug of choice in dogs: Dose: @ 25 mg/kg/day for three consecutive days.
Albendazole: Cat: Dose: @ 50 mg/kg for 21 days.
Fenbendazole: Dog: Dose: 50 mg/kg twice daily for 10 days (for adult flukes).
Bithionol: Effective at high doses, but efficacy is unpredictable (produces undesirable side effects).

Therapeutic control is the practicable method of minimizing trematodal infestation in livestock. Antitrematodal treatment is recommended at the start of monsoon and early summer season. This reduces the passage of eggs, contamination of grazing areas and thus the chances of infection of grazing livestock. The drugs that are ineffective against the immature or young flukes need to be repeated on a later date, so that the young ones are matured and eliminated subsequently. The livestock should not be allowed to graze near or on marshy areas, where the intermediate host of flukes habitats (snails). Use of molluscicides helps in elimination of the snails. The molluscicides are Copper pentachlorophenate (@ 11 kg/ha), Copper sulfate (5% @ 10 kg/ha) and pentachlorophenol.

## EXERCISE

1. Describe the general mode of action of anthelmintics with suitable drug examples.
2. **Write a short notes on the following:**
   a) Biochemical mechanisms of anthelmintic action
   b) Neuromuscular mechanisms of anthelmintic action
   c) Anthelmintic tolerance
   d) Ideal anthelmintic
3. **Give the source of the following:**
   a) Avermectins
   b) Milbemycin D
   c) Hygromycin B
   d) Kamala
   e) Male fern
   f) Nicotine
   g) Arecoline
4. **Describe the mechanism of action of the following drugs:**
   a) Piperazine
   b) Benzimidazoles
   c) Levamisole (anthelmintic)
   d) Ivermectin
   e) Carbon tetrachloride
   f) DEC
   g) Niclosamide
   h) Praziquantal
   i) Diamfenetide
5. **Give the line of treatment of the following:**
   a) Roundworms in dog/pig/calf
   b) Hookworms in sheep
   c) Strongyloidosis in a horse
   d) Lungworms in a cow
   e) Tapeworms in poultry/calf/dog
   f) Fasciolosis (mature flukes) in sheep
   g) Fasciolosis (immature flukes) in a cow
   h) Adult heartworm in dog
6. **What do you mean by the following? Answer in one or two sentences for each:**
   a) Vermifuge
   b) Vermicide
   c) Endectocide
   d) Taenifuge
   e) Taenicide
   f) Molluscicide
7. **Matching** (Parallel pairs)/**Multiple choice** (Right choices):
   a) Inhibition of worm fumerate reductase: Cambendazole/Fenbendazole/Levamisole/Bithionol/ Hexachlorophene
   b) Cambendazole/Fenbendazole: Inhibition of fumerate reductase/Inhibition of glucose transport
   c) Inhibition of parasite tubulin polymerization: Mebendazole/Flubendazole
   d) Uncouple worm oxd. phosphorylation: Salicylanilides/Substituted phenols/Halogenated hydrocarbons
   e) Uncouple worm oxd. Phosphorylation: Niclosamide/Rafoxanide/Closantel/Disophenol/Nitroxynil

f) Inhibition of worm glycolysis: Thiacetarsamide/Potassium antimony tartarate/Stibophen/Clorsulon
g) Clorsulon: Antitrematodal sulfonamide
h) Nicotinic action on worms: Levamisole/Morantel/Bephenium
i) OP anthelmintics: AntiChEs/Coumaphos/Haloxon/Dichlorvos/Trichlorphon
j) Worm muscle hyperpolarizers: Piperazine/Avermectins
k) GABA agonist anthelmintic: Ivermectin/Abamectin/Moxidectin/Milbemycin/Piperazine
l) Diethylenediamine anthelmintic: Piperazine
m) Piperazine: Antinematodal/Anticholinergic/Blocks succinic acid synthesis/GABA agonist
n) Phenothiazine: Thiodephenylamine anthelmintic/Photosensitization keratitis
o) Phenothiazine sulfoxide: Photodynamic/Photosensitization keratitis
p) Benzimidazole not an inhibitor of fumerate reductase in worms: Flubendazole/Mebendazole
q) Benzimidazole inhibitor of fumerate reductase in worms: Cambendazole/Fenbendazole
r) Albendazole: Broad anthelminic/Antinematodal/Antitrematodal/Anicestodal
s) Albendazole: Sulfones and sulfoxide
t) Embryotoxic benzimidazole: Albendazole/Cambendazole/Parbendazole/Oxibendazole
u) Teratogenic benzimidazole: Parbendazole/Cambendazole/Albendazole
v) Nonembryotoxic benzimidazole: Flubendazole/Mebendazole/Luxabendazole/Fenbendazole
w) Nonteratogenic benzimdazole: Luxabendazole/Mebendazole/Fenbendazole/Oxfendazole/Flubendazole/ Luxabendazole/Thiophanate
x) Broad spectrum benzimidazole anthelmintic: Albendazole/FenbendazoleOxfebdazole/Netobimin
y) Benzimidazole effective only against round and tape worms: Cambendazole/Mebendazole/Luxabendazole
z) Benzimidazole effective only against round worms and flukes: Luxabendazole
a) Benzimidazole as antinematodal only: Parbendazole/Flubendazole/Thiophanate/Febantel
b) Benzimidazole prodrug: Febantel/Netobimin/Thiophanate
c) Febantel: Fenbendazole prodrug
d) Netobomin: Albendazole prodrug
e) Thiophanate: Lobendazole prodrug
f) Anthelmintic antibiotic: Hygromycin B
g) Imidazothiazone anthelminitic: Butamisole/Tetramisole/Levamisole
h) Tetrahydropyrimidine anthelmintic: Pyrantel/Morantel
i) Trichlorphon: Dichlorvos prodrug/Insecticide/Anthelmintic
j) Ivermectin: Ectoparasiticide/Endoparasiticide/Endectocide
k) Injectable antihookworm drug: Disophenol
l) Thenium closylate: Mature and immature hookworms
m) Prevention of heartworm infestation in dogs: DEC
n) Natural anticestodal agent: Pumpkin seeds/Male fern/Kamala/Nicotine/Arecoline
o) Natural taenifuge: Pumpkin seeds/Male fern/Kamala/Arecoline/Nicotine
p) Taenicide: Tin compounds/Lead arsenate/Bunamidine/Niclosamide/Dichlorophen
q) Uredophos: Antinematodal/Anticestodal/OP compound
r) Niclosamide: Anticestodal/Antitrematodal
s) Dichlorophen: Taenicide/Bactericidal/Fungicidal
t) Cestocidal benzimidazole: Mebendazole/Fenbendazole/Oxfendazole/Albendazole
u) Effective against both adult and young *F. hepatica* : Clioxanide/Niclofolan/Rafoxanide/ Bromophenophos /Clorsulon
v) Effective against adult flukes: Nitroxynil/Oxyclozanide/Bithinol sulfoxide
w) Bromosalans: Effective against juvenile flukes and adult flukes
x) Endoectocide: Closantel/Ivermectin
y) Principally used against immature flukes: Diamfenetide
z) Against both mature and immature flukes: Triclabendazole
a) Drug in paramphistomiasis: Niclosamide/Resorantel/Bithionol
b) Drug in paragonimiasis: Praziquantel/Albendazole/Fenbendazole/Bithional
c) Drug in paraimphistomiasis and paragonimiasis: Bithional
d) Benzimidazole used in paragonimiasis: Albendazole/Fenbendazole
e) Molluscicide: Cu pentachlorophenate/Cu sulfate/pentachlorophenol
f) Trichlorphon: Dichlorvos

8. **Give the most appropriate reason of each of the following statements:**
a) Highly effective anthelmintic should not be used for prolonged schedules.
b) Cross anthelmintic tolerance is observed for benzimidazoles.
c) Rotational approach of using anthelmintics must be followed.
d) Total elimination of helminth infestation in animals is not desirable.
e) Host tissue persistence of anthelmintics is both desirable and undesirable.

f) Cambendazole/Fenbendazole is effective against helminthes which lack fumerate reductase.
g) Salicylanilides/Substituted phenols/Halogenated hydrocarbons are fairly toxic to the host.
h) Niclosamide/Rafoxanide/Closantel/Disophenol/Nitroxynil is fairly toxic to the host.
i) Anthelmintics interfering with neuromuscular transmission act as vermifuges.
j) Imidazothiazides/Pyrimidines/Bephenium cause (s) spastic paralysis of worms.
k) OP compounds act as anthelmintics.
l) OP anthelmintics/Coumaphos/Haloxon/Dichlorvos is/are relatively safe to the host.
m) Piperazine/Avermectins cause flaccid paralysis of worms.
n) Phenthiazine/Benzimidazoles are used for control of helminth infestation in livestock.
o) Concurrent use of penothiazine and OP compounds as anthlmintics should not be done.
p) Phenothiazine is contraindicated in terminal pregnancy, but not in early pregnancy.
q) Phenothiazine as anthelmintic is to be avoided in dairy cows.
r) Phenothiazine use in sheep for wool as anthelmitic is to be avoided.
s) Albendazole is a broad spectrum anthelmintic.
t) Albendazole also exerts antitreamatodal as well as anicestodal drug.
u) Thiabendazole is a popular anthelmintic among the farmers.
v) Levamisole replaced tetramisole as anthelmintic.
w) Levamisole is the commonly used anthelmintic in livestock.
x) Levamisole as anthelminitic is preferred in immunologically compromised animals.
y) Pyrantel tartrate is effective in the treatment of pinworm infestation in dogs.
z) Pyrantel should not be used along with cholinergics.
a) Avermectins though chemically related to macrolide or polyene antibiotics differ in biological activity.
b) Ivermectin is an endocctocide.
c) Closantel is an endectocide
d) Thiacetarsamic is effective against heartworm of dogs, but toxic to the host also.
e) DEC is not safe for use in dogs until they are cleared of microfilariae.
f) Tetrachloethylene as antinematodal should not be used in tapeworm infested animals.
g) Lead arsenate exerts anticestodal action.
h) Praziquantel is unique in exerting anticestodal activity.
i) Carbon tetrachloride is no longer used as an antitreamatodal drug in livestock.
j) Closantel has a very wide range of biological activity.
k) Closantel has broad range anthelmintic activity.
l) Use of dichlorvos as anthelmintic in dogs causes salivation and loose feces.
m) Disophenol affects only the blood sucking worms/hookworms.
n) Use of ivermectin poses ecological threat.
o) Phenothiazine-treated animals should be kept indoors for at least two days.
p) Thiabendazole/Coumaphos/Oxyclozanide can be used in dairy cows.
q) Hexachlorophene/Oxyclozanide is ineffective against immature flukes.
r) Ivermectin is not effective against flukes and tapeworms.
s) Ivermectin does not affect host's nervous system.
t) Anthelmintics effective against only adult worms should be repeated.
u) Anthelmintics are great value in AH practices.
v) Though phenothiazine is toxic, still it is a drug of value in horses.
w) Hygromycin B is intermittently administered to pigs.
x) Vermifuges are generally combined with a purgative.
y) Oxyclozanide is a better fasciolicidal than hexachlorophene in ruminants.
z) Diamfenetide is less effective agmst mature liver flukes.
aa) Triclabendazole is the drug of choice in fascioliosis in cattle and sheep.
bb) Dose of levamisole is just half to that of tetramisole.
cc) Pharmacologically trichlorfon is similar to dichlorvos.
dd) For heartworm prophylaxis ivermectin is preferred to DEC.
ee) Elimination of heartworm microfilariae is essential before giving DEC in dog.
ff) Trichlorphon is a prodrug.

9. **Matching** (Special for all **Chemotherapy**: Parellel pairs):
a) Acyclovir: DNA polymerase (inhibition)
b) Zidovudine: Reverse transciptase/RNA dependent DNA polymerase (inhibition)
c) Zidovudine: Thymidylate kinase (inhibition)
d) Antiretroviral drugs: RNA dependent DNA polymerase (inhibition)
e) Penicillins: Penicillinase/Beta-lactamase (breakdown)
f) Cephalosporins: Cepholosporinase/Beta-lactamase (breakdown)

g) Clavulinic acid/Sulbactum/Tazobactam: Beta-lactamase (inhibition)
h) Fluoroquinolones/Quinolones: DNA-gyrase (inhibition)
i) Rifampin: DNA dependent RNA polymerase (inhibition)
j) Cefamycins: Beta-lactamases (breakdown)
k) Carbapenems/Monobactams/Imipenem/Aztreonam: Beta-lactamase (resistant)
l) Methotrexate: Dihydrofolate reductase (inhibition)
m) Hydroxyurea: Ribonucleotide reductase (inhibition)
n) Sulfonamides/Dapsone/PASA: Dihydropteroate synthetase (Inhibition)
o) Carbapenems/Imipenem: Dehydropeptidase I (renal tubular breakdown)
p) Cilastin: Dehydropeptidase I (inhibition)
q) Rifampin/Chloramphenicol/Ketoconazole: Microsomal enzymes (inhibition in host)
r) Leavamisol/Amphotericin B: Immunostimulant (host)
s) Tetracyclines/Chloramphenicol: Immunosuppressant (host)
t) Penicillins/Cephalosporins/Cephamycins/Carbapenems/Monobactams: Transpeptidase (inhibition)
u) D-Cycloserine: d-ala-d-ala synthetase (inhibitor)
v) Flucytosine: Cytosine deaminase (formation of 5-FU)
w) 5-Fluorouracil: Thymidylate synthetase (inihibition)
x) Cytarabine/Vidarabine: DNA polymerase (inhibition)
y) Dactinomycin: Topoisomerase II (stabilization)
z) Etoposide: Topoisomerase II (activation)
aa) Anthracycline antibiotics/Doxorubicin/Daunorubicin: Topoisomerase II (stabilization)
bb) Aminoglycosides: Aminoglycosidase (resistance)
cc) Chloamphenicol: Chloramphenicol acetyltransferase (resistance)
dd) Albendazole/Thiabendazole/Levamisole/Bithionol/Hexachlorophene: Fumerate reductase (inihibtion)
ee) Thiacetarsamide/Pot.Antimony tartrate/Stibophen: Phosphoglycerate kinase (interference)
ff) Thiacetarsamide/Pot.Antimony tartrate/Stibophen: Phosphoglycerate mutase (interference)
gg) Coumaphos/Haloxon/Dichlorvos/Trichlorphon/Ureophos: AChE (inhibition)
hh) Proguanil/Cycloguanil/Pyrimethamine: Dihidrofolate reductase (inhibition)
ii) Streptomycin/Spectinomycin/Tetracyclines:30S ribosomal subuint
jj) Chloramphenicol/Thiamphenicol/Florfenicol/Macrolides/Lincosamides: 50S ribosomal subunit
kk) Aminoglycosides (except streptomycin): 30S ribosomal subunit and 30S-50S ribosomal interface.
ll) Vincristine/*Vinca* alkaloids: Microtubules (anticancer)
mm) Mebendazole/Flubendazole: Microtubules (anthelmintic)
nn) Griseofulvin: Microtubules (antifungal)
oo) Paclitaxel/Docelatel: Microtubules (freezing, anticancer)

# Chapter – 40: ANTIPROTOZOAN DRUGS

## 1. Anticoccidial Drugs

Coccidiosis is an important disease of domesticated animals and birds caused by an intestinal protozoan parasite *Coccidia.* The disease in seen in poultry, cattle, sheep, goat, pig, dog and cat. Coccidiosis has gained prominence due to enormous economic losses inflicted to the livestock industry, particularly to the poultry industry.

### Dugs used in Avian Coccidiosis (Anticoccidials)

Coccidiosis is one of the most prevalent diseases in poultry birds mainly caused by various species of *Eimeria* which affect various sites in the intestine. In poultry the disease is characterized by anorexia, reduced growth rate, loss of body weight, decreased egg production, haemorrhagic diarrhoea and high morbidity and mortality. The control of coccidiosis in poultry is achieved by vaccination and/or prevention and treatment with anticoccidial drugs. Anticoccidials are almost universally used in broilers prophylactically throughout their growing periods to achieve total continual prevention or suppression of coccidiosis.The establishment of protective level of immunity in these short lived (42 days) birds is not considered as exposure to the organism involves temporary setback in growth and feed conversion. But the use of anticoccidials in layers and breeders is not as universal as broilers and for these long lived birds immunization is more often used for reasons of safety and economy. In these birds, a low level of anticoccidial is used in feed up to 14 weeks, allowing the birds to be exposed to immunizing infection while guarding against acute outbreaks. Another approach in these birds is planned vaccination by exposing day-old or older chicks to low doses of live sporulated oocysts of various *Coccidia* (Coccivac) in feed or drinking water. A therapeutic level of an anticoccidial drug should be given to control acute outbreaks. Continuous use of anticoccidials promotes development of drug resistant strains and to combat this, two or more anticoccidials are commonly used sequentially.

Two programmes are adopted for the above purpose: **Shuttle Programme**: Change of anticoccidal drug from one to another in a single grow-out. **Rotation Programme**: Change of anticoccidial between two grow-outs.

The effect of anticoccidial drug may be **coccidiostatic** (arresting growth and development) or **coccidiocidal** (killing effect). Most anticoccidials currently used in poultry are coccidiocidal. In the seven-day life cycle of poultry *Coccidia*, there are two asexual stages of 4-5 days duration and a sexual cycle of two days and oocyst sporulation outside the host require another 1 or more days. All anticoccidials show their maximum efficacy at the earlier stages against the first or second asexual cycle. So, anticoccidials must be used prophylactically (as most damage occurs before clinical signs manifest and drug cannot completely stop outbreak) instead therapeutically. Anticoccidials are used in feed for prophylaxis and water medication is preferred over feed medication for therapy. In general their withdrawal period in broilers is 3-7 days prior to slaughter.

### a. Drugs in Avian Coccidiosis:

**Classification**:

| Chemical Group | Anticoccidial Drugs |
|---|---|
| Dimethyl pyridinol | Clopidol |
| Quinolones | Decoquinate, Buquinolate, Nequinate and Methyl benzoquate |
| Polyether antibiotics (Ionophores) | Monensin, Lasalocid, Salinomycin, Narasin, Maduramicin and Semduramicin |
| Guanidine | Robenidine |
| Thiamine antagonist | Amprolium** |
| Nitrobenzamide | Dinitolmide |
| Dinitrocarbanilide | Nicarbazin |

| | |
|---|---|
| Benzylpurine | Arprinocid |
| Benzene acetonitriles | Clazuril and Diclazuril |
| Traizinones | Toltrazuril* |
| Quinazolines | Halofuginone |
| Sulfonamides | Sulfadimidine*,Sulfachloropyrazine*, Sulfadimethoxine* and Sulfaquinoxaline** |
| Diaminopyrimidines | Ormetoprim, Ethopabate, Pyrimethamine and Diaveridine |
| Tetracyclines | Oxytetracycline** and Chlortetracycline* |

*used as curative only; ** used as curative as well as prophylactic. Others are only preventive

The important features of widely used anticoccidials along with their use and dosage schedule are given below:

**Clopidol and Quinolones**:
These are broad spectrum anticoccidials, mainly coccidiostatic, act on 1st day of life cycle of coccidian (hence no therapeutic value). They prevent the development of sporozoites and trophozoites of *Eimeria* by inhibiting the electron transport system within the coccidial mitochondria.
**Dosages**: All are used as preventive:
Clopidol (Clopindol): @ 0.0125% (125ppm) in feed, Withdrawal period (WP): Nil.
Decoquinate (Decox): @ 0.003% (30 ppm) in feed, WP: Nil.
Methyl benzoquate: @ 0.002% (20 ppm) in feed.

**Polyether Antibiotics (Ionophores)**:
Monensin is obtained from *Streptomyces cinnamonensis*; all have similar broad spectrum of anticoccidial activity. All are mainly coccidiocidal and act on first 2-days of life cycle, by preventing the development of trophozoites and first generation schizonts. All are able to form complexes with ions (ionophores) like $Na^+$, $K^+$ and $Ca^{++}$ (both in the host and parasite) and transport them into and through biological membranes. This results in inhibition of some mitochondrial functions. Higher doses of these drugs are also toxic to the chickens. Monensin may cause problems in feather growth, nutrient interactions (Monensin should not be combined with tiamulin as combination causes severe growth depression in poultry) and other toxic effects. Among the ionophores, lasalocid is the least toxic and maduramicin is the most potent anticoccidial.
**Dosages**: All are used as preventive:
Monensin (Coban). @ 0.010-0.012% (100-120 ppm) in feed, No WP.
Lasalocid (Avatec): @ 0.0075-0.0125% in feed, WP- 3 days.
Salinomycin (Saccox): @ 0.0044-0.0066% in feed, No WP.
Narasin (Monteban): @ 0.006-0.008%, in feed, No WP.
Maduramicin (Cygro): @ 0.0005- 0.0006% in feed, WP: 5 days.
Semduramicin: @ 0.0025% in feed, No WP.

**Robenidine (Robenz)**:
A guanidine derivative, shows peak activity on day two of life cycle of *Eimeria*. It allows initial development of coccidia up to first generation schizont, but prevents differentiation of merozoites from mature schizont. It gives unpleasant taste to the flesh of the broilers if not withdrawn five days before slaughter.
Dosage: @ 0.0033% in feed

**Amprolium (Amprol)**:
It is a structural analog of thiamine (Vitamin B1) and thus competitively inhibits the absorption of thiamine (essential for rapid multiplication and growth) by the parasite. At higher doses, drug may also cause reversible thiamine deficiency in the host also. Anticoccidial activity of amprolium is cancelled by excess dietary thiamine. The drug shows peak activity on day three of life cycle and act chiefly upon the first

generation schizont, preventing the differentiation of merozoites. It also suppresses sexual cycle (gametogony) and sporozoites. Amprolium is stable in broiler rations at room temperature. It is compatible with vitamins, minerals, antibiotics and other nutrients used in poultry ration. It is the only anticoccidial approved as feed additive in layer birds.
**Dosage**: Preventive: @ 0.0125% in feed, No WP; Curative: @ 0.0125-0.025% in water for 7-14 days, No WP.
**Combination with other drugs**: Amprolium (highly effective against caecal species of coccididia but less effective against intestinal species) is combined with sulfonamides/ethopabate (control intestinal coccidia more efficiently than caecal forms) to compensate each other anticoccidial actions.
**Dosage**: Amprolium (0.0125-0.025%) + Ethopabate (0.0004-0.0045), is used as preventive, No WP.

**Dinitolmide (Zoalene)**:
It is partially coccidiocidal, effective against all important species of chicken coccidia, especially against *E. tenella* and *E. necatrix*. Its peak action is seen on early day-3 of asexual stages of life cycle. It also prevents sporulation of oocysts.
**Dose**: Preventive: @ 0.004-0.0125% in feed, No WP.

**Nicarbazin (Nicarb)**:
It is an equimolecular complex of dinitrocarbanilide (DNC) and Hydroxy dimethyl pyrimidine (HDP). It is used against both caecal and intestinal coccidiosis in chickens. Its peak action is on second asexual stage (day-4) of life cycle. Because of toxic/side effect in layers (affects egg production and quality dramatically) and has limited commercial use.
Dosage: Preventive: @ 0.01255 in feed, WP-4 days.

**Arprinocid (Arpocox)**:
It has broad spectrum anticoccidial activity. It is a purine analog; acts by antagonizing purine metabolism. It blocks the hypoxanthine transport across the coccidial cell membrane and inhibits nucleic acid synthesis. Peak activity is seen on first or second day of asexual life cycle inhibiting sporozoites and trophozoites.
Dosage: Preventive: 0.0060% (60ppm) in feed, WP: 5 days.

**Diclazuril**: Preventive: @ 0.0001% in feed, No WP
**Toltrazuril**: Curative: @ 0.0025% in drinking water.

**Halofuginone**:
It has broad spectrum activity against *Eimeria* of chickens, turkeys and other animals. It shows peak activity against asexual stages of *Eimeria* and may be coccidiostatic or cidal.
Dosage: Preventive: @ 0.0003% in feed continuously, WP: 7 days.

**Folic acid antagonists**:
These drugs are mainly effective against intestinal coccidia as compared to caecal coccidia. They interfere with the folate metabolism and thus inhibit the synthesis of nucleic acids required during multiplication of coccidia (schizogony). **Sulfonamides** competitively antagonize PABA, a precursor of folic acid by inhibiting the coccidial enzyme dihydropteroate synthetase. **Diaminopyrimidines** inhibits coccidial DHFRase enzyme and thus prevent the conversion of dihydrofolate to tetrahydrofolate. Their peak action is seen on day four of life cycle. Sulfonamides are important because there are few alternatives for the treatment of upper intestinal coccidiosis. Combination of sulfonamides and diaminopyrimidines has synergistic action.
**Dosage**: Sulfadimidine: Curative: @ 0.2% in water for 4 days, WP: 10 days; Sulfadimethoxine: Curative: @ 0.05% in water for 6 days, WP: 5 days; Sulfachloropyrazine: Curative: @ 0.03% in water, for 3 days, WP: 5 days; Sulfaquinoxaline: Curative: @ 0.05% in feed and 0.04% in water. Preventive: @ 0.0125% in feed. Combination of Sulfaquinoxaline (0.0125%) + Ormetoprim (0.0075%) in feed as a preventive.

**Tetracyclines**:
Oxytetracycline and chlortetracycline have special anticoccidial action in chickens. These inhibit coccidial protein synthesis.
**Dosage**: Oxytetracycline: Curative: @ 0.022% in feed + 0.25% Calcium, for a maximum period of 5 days; Preventive: @ 0.022% in feed, WP: 5 days; Chlortetracycline: Curative: @ 0.022% in feed + 0.8% Calcium for a maximum period of 3 weeks, No WP.

**b. Treatment of Bovine Coccidiosis**
Two *Eimeria* species of coccidia viz.*E. bovis* and *E. zurnii* are known to cause clinical coccidiosis in bovines (particularly in calves) associated with symptoms of bloody diarrhea, anaemia, anorexia, dehydration and loss of body weight.
Drugs for **treatment and/or prevention** of coccidiosis in cattle:
Decoquinate in calves @ 0.5 mg/kg orally for 4 weeks.
Amprolium @ 10 mg/kg/day in feed or water or by drench for five successive days for treatment and @ 5 mg/kg/day for three weeks orally (in feed or water) for prevention.
Sulfamethazine @ 140 mg/kg orally for three days and @ 5 mg/kg/day in feed for 15 days for therapeutic and preventive measures in calves respectively.
Monensin @ 1 mg/kg or 0.006% in feed for about five weeks as a preventive measure.
Lasalocid @ 112 ppm in feed for 30 days for prevention.
Sulfaquinoxaline @ 13 mg/kg for 2-3 weeks for prevention.
Diiodohydroxyquinoline (Iodoquinol): 5 gm tablet/200 kg/day for 2-3 days as a therapeutic measure.
Nitrofurazone: Curative: @15 mg/kg/day orally for 7 days.

**c. Treatment of Ovine or Caprine Coccidiosis**
**Preventive**:
Sulfaguanidine @ 0.2% in feed or 3 gm/lamb/day for 20 days orally.
Monensin @ 20 mg/kg of feed for continuous feeding.
Lasalocid @ 22-33 ppm in feed for continuous feeding.
**Therapeutic**:
Amporlium @ 55 mg/kg twice daily for 20 days, orally
Sulfamethazine @ 140 mg/kg/day orally for 3 days.
Nitrofurazone @ 0.04% in feed for 7 days 0r 0.0133%in water for 7 days.
Monensin @ 2 mg/kg/day orally for 20 days.

**d. Treatment of Rabbit Coccidiosis**
Coccidiosis is one of the most serious diseases of rabbits. *E. stiedae* affect bile duct epithelium and some *Eimeria* spp affect intestinal epithelium.
**Preventive**:
Sulfaquinoxaline @ 0.025% in feed for 30 days or 0.1% for 2 weeks.
Sulfachloropyrazine @0.1% in drinking water from 1 month age to 2 months age.
**Therapeutic**:
Sulfadimethoxine orally @ 200 mg/kg 1st day followed by 100 mg/kg for 4 days.
Sulfaquinoxaline and sulfamerazine each @ 0.03% in drinking water for 10 days.

**e. Treatment of Canine Coccidiosis**
Coccidiosis can occur in kenelled puppies due to infection with *Isospora* spp. The drugs are
**Preventive**:
Amprolium: Medicated water (30ml 9.6% amprolium + 3.8 L drinking water) is to be given to pups daily for 7-10 days. Bitches are given only medicated water for 10 days before whelping. In thiamine deficiency, pups should be treated with thiamine, calcium and fluids.
**Therapeutic**:
Sulfadimethoxine: Oral or parenteral @ 55 mg/kg daily for 21 days.

## 2. Antibabesial Drugs

Babesiosis is a tick-borne protozoan disease of host (horse, cattle, sheep and dog) erythrocytes caused by *Babesia* and mostly prevalent in tropical and subtropical parts of the world.The disease is characterized by fever, haemoglobinuria, anaemia and icterus. The eradication of the disease is based on control of vector ticks, chemotherapy and in few countries, vaccination. However, there has been little progress in regards of development of vaccine against *Babesia* and the control of vector is also very difficult. Therefore, the control of disease is directed towards chemotherapy.

**Antibabesial drugs:** These include drugs which are used for the contol and trearment of babesiosis.

**Acridine derivatives (Acriflavine, flavin, euflavin):**

These drugs are effective against *B. equi* and used in horses as 5% solution IV @ 4-5 ml /100 kg ( 2-2.5mg/kg) and in bovines @ 2.2 mg/ kg,IV. Systemically these drugs are less toxic.

**Aromatic Diamidines**: Phenamidine isethionate and diminazene aceturate.

The antiparasitic activity of diamidines may be due to interference with the aerobic glycolysis as well as interference with synthesis of DNA in the parasite. Diminazene produces its antiparasitic action by selective blocking of kinetoplast DNA synthesis and replication.

**Phenamidine isethionate**: It is recommended for bovine, equine and canine babesiosis.

Dose: Horse & Cattle: @ 0.03ml of a 40% solution/kg (12mg/kg) SC single dose; Dogs: @ 0.3ml of a 5% solution/kg (15mg/kg), SC repeat after 5 days.

**Diminazene aceturate**: It is an odorless yellow powder relatively soluble in water. The drug has babesicidal, trypanocidal as well as bactericidal (mainly *Brucella* and *Streptococcus* spp) activities. The drug is used in the treatment of babesiosis in horses, cattle, sheep and dogs and the symptoms disappear within 24 hours of treatment. The drug has no prophylactic value.

Dose: Cattle, Sheep & Dog: @ 3.5 mg/kg, SC or IM; Horse: @ 5 mg/kg SC or IM for 2 consecutive days.

**Carbanilides**: These include:

**Imidocarb dipropionate**: It is used for the treatment and prophylaxis of both babesiosis and anaplasmosis. It acts directly on the parasite and causes an alteration in number and size of nuclei and morphology (vacuolation) of the cytoplasm.The drug is administered by SC or IM routes but not IV.

Dose: Therapeutic: Cattle: @ 1.2 mg/kg, single dose; Horse: @ 2.4 mg/kg, two injections at 24 hour interval; Dogs: @ 6 mg/kg, single dose. Prophylactic: Cattle: 3 mg/kg. Single injection gives protection for more than one month.

**Amicarbalide**: It is active against all *Babesia (B. divergens, B. bovis, B. bigemina, B. argentina and B.caballi)* of cattle and horses. It has no prophylactic value. It has low toxicity.

Dose: @ 5-10 mg/kg as 50% solution, SC or IM or slow IV, repeat after 24 hours if haemoglobinuria persists.

**Quinuronium sulphate**:

This is a complex urea compound and is the active component of a number of commercial antibebasial drugs (Acaprin, babesan, pirevan, piroparv and piroplasmin). The drug is effective against many large *Babesias (B. canis, B. bigemina and B. caballi)* and also against small *Babesia (B.bovis and B. argentina)* and were extensively used until the discovery of diamidines. A single dose of the drug is adm.by SC. These drugs have potent anticholiesterase activity and have low margin of safety. If the treated animal develop toxicity (salivation, panting, sweating, diarrhea and collapse), it should be immediately treated with atropine and adrenaline.

Dose: Cattle & horse: @ 1 mg/kg as 5% solution; Dogs: @ 0.25 mg/kg as 0.5% solution.

**Trypan blue**: An azo dye and one of the oldest remedies for babesiosis.It is effective against larger species of *Babesia*. It is used as 1% solution and must be given IV.

Dose: Dog: @ 5-10 ml, single dose; Cattle: 50-100 ml, single dose.

The drug is rarely used because it causes severe tissue sloughing on perivascular leakage, causes objectionable discoloration of the flesh of the treated animals and frequent relapse.

**A compound of phenazone and diminazene**: Consisting of the former as 8.75% and the later as 7% is very effective in the treatment of clinical babesiosis in horse, cattle, sheep and dog.
Dose : @ 0.05 ml/kg, IM or SC.
**Toxicity of antibabesial drugs:** All the antibabesial drugs are potentially toxic. Among these, imidocarb is least toxic than other followed by amicarbalide, diminazene and most toxic is quinuronium.Therapy with quinuronium may produce severe cholinergic toxic signs due to anticholinesterase activity. Repeated use of diminazene and phenamidine cause degenerative changes, in liver, kidney and heart.These drugs should not be used in debilitated animals or in animals with hepatic or renal insufficiency.

### 3. Antianaplasmic Drugs

Anaplasmosis is one of the most severe haemotropic diseases of cattle in tropical and subtropical countries of the world. The control of the disease is based on vaccination and chemotherapy, or a combination of both. Vaccination can be done by using killed anaplasma vaccine (cattle) or by using attenuated anaplasma vaccine (sheep). The later provides better protection against natural infections than the killed vaccine by inducing stronger and long lasting cell mediated immunity. However, the vaccines are not commercially available. Chemotherapy is important in the control of anaplasmosis.

**Tetracyclines**:
Tetracycline, chlortetracycline and oxytetracycline are equally effective against *Anaplasma marginale* in cattle and are used in the treatment of clinical anaplasmosis.
Dose: For treatment of acute anaplasmosis:
Minimum one IM injection of tetracyclines @ 6.6-11 mg/kg and slow transfusion of 2-4 L of blood.(Survivality is 100%, if early treatment is given before Hb value falls below 4 mg%).Or Long acting tetracyclines (L-200) single IM injection @ 20 mg/kg.
For elimination of carrier state: Chlortetracycline: @ 2.2 mg/kg, orally daily for 60 days; or long acting tetracyclines (L-200): @ 20 mg/kg, IM, two injection one week apart.

**Imidocarb**:
Originally introduced as an antibabesial drug. It is also found to be effective for the treatment of anaplasmosis and elimination of carrier state.It is orally ineffective and administered SC. It is as effective as tetracycline against bovine anaplasmosis but more economical. It is not approved in many countries because of suspected carcinogenic effect and long lasting residues.
Dose: Curative: @ 1.5 mg/kg, SC, single dose. For elimination of carrier state: @ 5 mg/kg, IM or SC, two injections 14 days apart. For prophylaxis: @ 3 mg/kg, IM or SC.

**Gloxazone**:
Chemically it is dithiosemicarbazone. It gives a temporary curative effect and relapse almost invariably occurs in cattle within one month of treatment. In therapeutic dose it is as effective as tertracycline.
Therapeutic dose: @ 5-10 mg/kg, IV, single dose.

### 4. Antitheilerial Drugs

The drugs available for the treatment of theileriosis in cattle are as follows:

**Tetracyclines**: Arrest the development of schizonts in lymphocytes and reduce invasion of parasite into new cells.
**Oxytetracyclin**: @ 15 mgIM daily for 5 days or @ 5-10 mg/kg IV 4-6 times daily.
**Rolitetracycline**: @ 4 mg/kg IM, 4 times daily for 14 days
**Long acting oxytetracycline**: 20 mg/kg IM every 4 days.

**Hydroxynaphthoquinones**:
**Menoctone**: Suppresses parasitaemia and causes degenerative changes in the macroschizonts. It is an expensive drug. Dose: Curative: @ 5-10 mg/kg, IM.
**Parvaquone**: Highly effective against *T. annulata*, especially against early infective stages. Dose: @ 20 mg/kg, IV as a single dose or @ 10 mg/kg IV, two injections at 48 hr intervals. The withdrawal period for meat is 21 days and milk discard time is 14 days.
**Bupervaquone (Butalex)**: Highly effective against *T. annulata*. It is the drug of choice in cattle and buffaloes. It is administered IM and should not be injected IV or SC.
Dose: @ 2.5 mg/kg, IM ( 50 mg/ml solution ). If necessary, a second injection is given after 48 hours.
The effective control of theileriasis involves an integrated approach of using bupervaquone and immunization.

**Quinozolines**:
**Halofuginone**: Effective in early stages of infection i.e. soon after the detection of the schizonts in lymph node biopsies. It is a schizonticidal. It produces mild diarrhea at therapeutic doses, but toxic at doses more than 3 mg/kg.
Dose: Curative: @ 1-2 mg/kg, orally, once.

The currently available drugs in the treatment of theileriosis are effective only against the schizont, but not the erythrocytic stage of the parasite. Hence, the drug therapy is of limited value. Effective tick control measures (against *Hyalomma anatolicum anatolicum*) help in minimizing the outbreaks of theileriasis.

## 5. Trypanocidal Drugs

These are the drugs which are used for the control and treatment of trypannosomiosis.

**Aromatic diamidines**: This group of drugs has activity against both *Trypanosoma* and *Babesia*.The important member of this group are: Phenamidine, Stilbamidine, Pentamidine and Diminazene.
**Phenamidine**: It is used both in the treatment of babesiosis and trypanosomiasis, has strong action against *T.brucei* and *T. evansi*.The dose and adm. are same as discussed in the antibabesial drugs.
**Stilbamidine and Pentamidine**: Stilbamidine is used in human trypanosomiasis caused by *T.vivax* but less toxic pentamidine is now preffered. Neither is now used in veterinary purposes.
**Diminazene aceturate (Berenil)**: The drug has trypanocidal, babesicidal and also bactericidal activity. As a trypanocidal it is active against *T.vivax, T. congolense and T. brucei*. Berenil has little prophylactic value.
Dose: Cattle, horse, sheep & goat: For the treatment of *T.vivax* and *T. congolense* infections: @ 3.5 mg/kg as 7% solution (0.05 ml/kg), IM or SC; for *T. brucei*: @ 7 mg/kg.

**Aminophenanthridium compounds:** This group includes:
**Homidium (Ethidium)**: Trypanocidal against *T. congolense, T vivax and T. brucei* but not active against *T.evansi*.
Dose: All species: 1 mg/kg, deep IM, single dose. The single dose also protects animals from infection for one month.

**Isometamidium (Samorin)**. Trypanocidal against *T. congolense* and *T. vivax* (cattle and horses) and *T. evansi* (cattle, buffaloes and camels). It has better prophylactic value than homidium and gives protection upto 6 months. The drug is administered deep IM, but local irritation, pain and necrosis may occur at the site of injection.
Dose: @ 0.5 mg/kg, deep IM (@ 1 mg/kg for resistant strain) as curative and @ 2 mg/kg as prophylactic.

**Quinapyramine compounds**:
These are effective against *T. congolense, T. evansi, T vivax, T. equiperdum, T. equinum. T. brucei* is less affected. The action is due to inhibition of growth and cell division of trypanosomes. Two compounds are used:
**Quinapyramine sulphate** (water soluble, rapidly absorbed, mainly trypanocidal, provide short but rapid therapeutic action, has low prophylactic value) and **Quinapyramine chloride** (very less water soluble, slowly absorbed, long acting, has strong prophylactic effect). These two salts are combined together and is called **"Antrycide prosalt"** (Trypacide, Tribexin), extensively used for the therapy and prophylaxis of trypanosomiasis. The sulphate provides initial protection while the chloride salt continues protection after the action of sulphate has disappeared. The treated animal may show salivation, shivering and increase in respiration and heart rate.Toxicity is common in young animals.
Dose: Young animals, less than 150 kg: 4.5 mg/kg; 150-200 kg: 1 gm; 200- 350 kg: 1.5 gm; More than 350 kg: 2 gm injected SC as 10% solution. In horse, to avoid sloughing, it is adm. IM (as 5% solution) or injected SC (as10% solution) in 2-3 sites.

**Suramin**:
It is highly effective against *T.evansi* (horses, camels, cattle and dogs), *T.brucei* (hoses, cattle and dogs) and *T. equinum* (horses). The drug is ineffective against *T.congolense and T. vivax*. It has maximum curative and less prophylactic action. Suramin is toxic and has low therapeutic index. Horses and donkeys are most susceptible to the toxic effect. It may cause degenerative changes in liver, kidney, spleen and adrenal glands.
Dose: Curative: Horse: 7-10 mg/kg,SC, 3 injections at weekly intervals; Camel: 8-12 mg/kg, SC, 3 injections at weekly intervals; Cattle : 12 mg/kg, SC, 3 injections at weekly intervals. Prophylactic: All species: 1-2 gm repeated at 10 days intervals. The drug is administered as 10% solution.

**Other Trypanocides**: These are earlier remedies for trypanosomiasis:
**Antimony potassium tartrate**: It is rarely used nowadays because of its toxicity.
Dose: Cattle and horse: 3-5 mg/kg, slow IV; Dog and cat: 1-3 mg/kg, slow IV.
**Anthiomaline**: It is less toxic than antimony potassium tartrate. Dose : 3-6 g/100 kg IM or SC.
**Trypan red and trypan blue**: These are neither safe nor as effective as modern drugs and are not used.

## 6. Antimalarial Drugs

These are the drugs used for the treatment, prophylaxis and prevention of relapse of malaria. Malaria is caused by different species of the protozoal parasite *Plasmodium* and is endemic in most of the tropical countries including India.

**The antimalarial drugs can be classified as follows**:
**A. Based on chemical structure**:

| | | |
|---|---|---|
| 1. Cinchona alkaloid | : | Quinine |
| 2. 4-Aminoquinolines | : | Chloroquine, Hydroxychloroquine and Amodiaquine |
| 3. 8-Aminoquinoline | : | Primaquine |
| 4. Acridine | : | Mepacrine |
| 5. Biguanides | : | Proguanil (Chloroguanide) |
| 6. Diaminopyrimidines | : | Pyrimethamine, Trimethoprim |
| 7. Quinoline methanol | : | Mefloquine |
| 8. Sulfonamides and sulfones | : | Sulfadoxine, Sulfamethopyrazine, Dapsone. |
| 9. Tetracyclines | : | Tetracycline, Doxycycline |
| 10. Newer drugs | : | Artemisinin, Halofantrine. |

**B. Based on site or stage of action of drugs in the life cycle of malarial parasite:**

**1. Drugs acting on site I**: Interfere with the development of schizonts in the red cells (Blood schizonticidal drugs): These drugs are used to treat an acute attack resulting in clinical cure and also used for suppressive prophylaxis of malaria: Quinine, Chloroquine, Mefloquine, Sulfonamides and sulfones, Tetracycline and Doxycycline, Artemisinin, Halofantrine.

**2. Drugs acting on site II**: Interfere with the development of schizont in liver (Tissue schizonticidal drugs): Drugs which attack this extraerythrocytic stage (hypnozoites) effect radical cure and given together with a clinical curative to achieve total eradication of the parasite from the patient body. A radical curative is essential in relapsing malaria: Primaquine.

**3. Drugs acting on site III**: Interfere with entry of merozoites from liver cells into red cells: The preerythrocytic phase (in liver) which is the cause of infection and clinical attack is the site of action of these drugs and are chemoprophylactics or causal prophylactics: Chloroquine, Proguanil, Pyrimethamine, Mefloquine, Sulfadoxine, Sulfamethopyrazine and Doxycycline.

**4. Drugs act on site IV**: Interfere with formation of gametocytes (Gametocidal drugs): The action of these drugs has no benefit to the treated patient but prevent the transmission to mosquito: Primaquine, Proguanil and Pyrimethamine.

The effective approaches to antimalarial therapy include therapeutic applications of antimalarial drugs acting at the four sites or stages of life-cycle of malarial parasite.The eradication programme should also include effective control of mosquito breeding by using insecticides and larvicides.

**Quinine**:

Quinine is a levo-rotatory alkaloid obtained from the bark of *Cinchona officinalis*. It is less effective and more toxic thal chloroquine. It exerts schizonticidal action by binding to a parasite pigment haemazoin and possibly by intercalating the DNA of the schizont.The drug is used in the treatment of resistant *Plasmodium falciparum* malaria ( 8 mg /kg tid for 7 days alone or with pyrimethamine 75 mg + sulphadoxine 1500 mg) and in cerebral malaria.

**4-Aminoquinolines**:

Chloroquine is the most commonly used 4-aminoquinolones.It is an erythrocytic schizonticide for all species of *Plasmodia*. It is the drug of choice for clinical cure ( 600 mg stat followed by 300 mg after 8 hrs and 300 mg daily for next 2 days, orally)and suppressive prophylaxis of all types of malaria, except that caused by resistant P. falciparum. It is a weak base which gets concentrated in the acidic vacuoles of the blood schizonts and interferes with degradation of hemoglobin by parasitic lysosomes. It inhibits the conversion of toxic haem to nontoxic parasite pigment, haemazoin.The haem then causes damage of plasmodial membrane.It is also effective in giardiasis, and amoebiasis. In addition, it has anti-inflammatory, antihistaminic, local anaesthetic and antiarrthymic effect. Hydroxychloroquine and amodiaquine are similar to chloroquine in antimalarial action but are less toxic.

**8-Aminoquinolines**:

Primaquine is effective against the exo-erythrocytic stage of *P. falciparum, P. vivax and P. ovale*. It is the most effective antimalarial drug as a gametocidal agent for controlling the transmission of the disease. Its mechanism of action is different from chloroquine but not exactly known. It affects the mitochondrial function in hepatocytic form of the parasite. Its main indication is for the radical cure of relapsing malaria (15 mg daily for 2 week, orally) with a full curative dose of chloroquine (to eliminate erythrocytic stage).

**Quinoline methanol**:

Mefloquine is a blood schizonticidal drug,effective against chloroquine sensitive as well as resistant plasmodia.Its use is restricted for multiresistant *P. falciparum* (@ 15 mg/kg, single dose, orally, pc, with plenty of water) because of its high toxicity and cost. It also gets concentrated in schizonts, bind to heam and complex causes damage of the membranes of the parasite.

**Proguanil**:
It is metabolized in the body to cycloguanil which inhibits preferably plasmodial dihydrofolate reductase (DHFRase) than the the mammalian enzyme. Presently its use is restricted for prophylaxis of malaria (100mg daily) in combination with chloroquine (300 mg weekly) upto 6 weeks of exposure.

**Pyrimethamine**:
Its selective antimalarial action is due to direct inhibition of plasmodial DHFRase enzyme.It is not used for the treatment of acute malaria alone because of its slow action but sometimes used as a prophylactic @ 25 mg weekly for 10 weeks.

**Pyrimethamine-sulfonamide/dapsone combination**: Sulfonamide and dapsone (PABA antagonists) alone are not effective antimalarial drugs, but when they are combined with pyrimethamine (inhibitor of DHFRase) a supra-additive effect is produced due to sequential blockade in folate synthesis in the parasite and used as a clinical curative. One tablet contains Sulfadoxine 500 mg + pyrimethamine 25 mg. Dose: Curative: Adult: 3 tablets, single dose; children 9-14 yr: 2 tablets; 4-8 yr: 1 tablet; 1-4 yr: ½ tablet.

**Artemisinin**:
Artemisinin is a sesquiterpine lactone and active principle of the plant *Artemisia annua*; also used in Chinese traditional medicine as 'Quinghaosu'. It has blood schizonticidal action in acute attack of both vivax and faciparum malaria including *P.falciparum*, which are resistant or sensitive to all other antimalarial drugs.Two derivatives of artemisinin viz. artemether (soluble in oil) and artesunate (soluble in water) are used. Both are prodrug and converted into active metabolite, dihydro-artemisinin. Artemisinin interact with haem in the parasite and causes generation of a free radical moiety that binds to plasmodial membrane protein and damages the parasite.This drug has restricted use in the treatment of acute attacks of multiresistant falciparum malaria
(Artesunate: Oral: @ 4 mg/kg on 1st day followed by @ 2 mg/kg per day in 1 or 2 doses for 5 days. Parenteral: 120 mg IV or im on 1st day followed by 60 mg daily for 4 days) where quinine is also not effective.

**Halofantrine**:
It is a blood schizonticide and action is similar to mefloquine. It has no action on gametocytes or hepatic phases of malarial parasite. It is used only for multiresistant falciparum malaria, if no other alternative is available. Dose: @ 8mg/kg, 3 doses at 8 hr intervals.

## 7. Treatment of Other Protozoan Diseases

### a. Antihistomonials

These are drugs effective against histomoniasis caused by *Histomonas meleagridis*. The drugs used in the treatment of histomoniasis are:

1. **Arsenicals**: used extensively in turkeys but now replaced by newer and more effective products.
   Carbasone: @ 250-375 ppm in feed; Nitarsone: @ 187.5 ppm in feed.
2. **Aminonitrothiazole**: Curative: @100 mg/bird after feeding (in capsule) or 0.1% in feed for 14 days.
   Prophylactic: @ 0.05% in feed or 0.03% in water for 5-6 months. The drug is nephrotoxic and plenty of water should be available to the birds to prevent the toxic effects.
3. **Nithiazide**: It is used for prevention and treatment of histomoniasis in poultry.
   Dose: For treatment: Medicated feed (0.04%) for a week, followed by prophylactic feeding (0.025%) for 2-3 weeks more; for prophylaxis in turkeys: 0.04% is required.
4. **Nitroimidazoles**:
   **Dimetridazole**: Has both therapeutic and prophylactic value. It should not be given to laying birds.
   Dose: Curative: 600-800 ppm in feed for 7 days; Prophylactic: 150-200 ppm in water for 7 days.
   **Ipronidazole**: It is more effective. Dose: Curative: 250 ppm in water; Prophylactic: 62.5 ppm in feed.
   **Ronidazole**: Highly effective @ 60 ppm in feed or water.

Following treatment with the above drugs, the withdrawal period for meat and egg is about a week.

**b. Drug used in the treatment of Giardiasis, Trichomoniasis, Amoebiasis and Balantidosis**

**Metronidazole**: It is effective against *Giardia, Trichomonas, Entamoeba histolytica* and *Balantidium coli.* It is well absorbed orally. It should not be given during pregnancy or to nursing bitches.
Dose: For canine and primates intestinal protozoa: @ 50 mg/kg/day orally for 5 days.
For treatment of trichomoniasis: Cattle: @ 75 mg/kg, iV, three times at 12 hr intervals.
Topical/Local application: As 5% ointment or 5% solution for intravaginal or intrauterine infusion.

**Quinacrine hydrochloride**: It is useful in the treatment of giardiasis in dogs, given orally as tablet or as IV or IM injection. Dose: Dogs: Orally: Large breeds: 200 mg / dogs 3 times on 1st day and twice daily for next 6 days; Small breeds: 100 mg twice on 1st day and once daily for next 6 days; Puppies: 50 mg twice daily for 6 days.

EXERCISE

1. Discuss the principles of chemotherapy of protozoan diseases of animals, including poultry and describe in brief the general mode of action of antiprotozoan drugs.
2. Discuss the principles of control and treatment of coccidiosis in poultry and describe the mode of action of anticoccidial drugs.
3. Enlist the most commonly used anticoccidials in poultry and describe in brief their mode of anticoccidial action.
4. Enlist the commonly used coccidostats and cocciocidal drugs in poultry. Describe what approaches you will adopt to control coccidiosis in a poultry farm.
5. Enumerate the different classes of drugs used in treatment of hemoprotozoan diseases of livestock. Discuss how you control theileriosis in cattle.
6. **Write a short note on the following:**
   a) Polyether anticoccidials
   b) Antimetabolite anticoccidials
   c) Anticoccidial Antibiotics
   d) Antibabesial drugs
   e) Antianaplasmic drugs
   f) Antitheilerial drugs
   g) Trypanocidal drugs
   h) Antimalarial drugs
   i) Antihistomonials
7. **Differentiate between the following**
   a) Shuttle programme and Rotational programme
   b) Coccidiostat and coccidiocidal
   c) Antimalarial gametocidal and schizonticidal drugs
8. **Give the chemotherapeutic use of each of the following drugs, mention the dose, route and frequency of administration (in any one species):**
   a) Maduramicin
   b) Amprolium
   c) Arprinocid
   d) Sulfaquinoxaline (anticoccidial)
   e) Diminazene aceturate
   f) Phenamidine isethionate
   g) Imidocarb propionate
   h) Quinuronium sulfate
   i) Chlortetracycline (Anaplasmosis)
   j) Oxytetracycline (Avian coccidosis)
   k) Bupervaquone
   l) Homidium
   m) Antrycide prosalt
   n) Suramin
   o) Metronidazole (in dogs)
   p) Anthiomaline
   q) Quinapyramine
9. **Which drug you recommend for the treatment of the following? Give its dose, route and frequency of administration:**
   a) Coccidosis in egg laying hens (curative)
   b) Prohylactic anticoccidial in broilers
   c) Coccidosis in a bull (curative)
   d) Anaplasmosis in a cow
   e) Babesiosis in a mare
   f) Trypanosomiasis in a stallion
   g) Histomoniasis in poultry
   h) Babesiosis in lambs
   i) Theileriosis in a bull
   j) Giardiasis in a bitch
   k) Coccidosis in a rabbit
   l) Theileriosis in a buffalo
10. **Describe the mode of action of the following drugs:**
    a) Polyether antibiotics as anticoccidials
    b) Sulfonamides/Ormetropim as anticoccidial
    c) Chloroquine
    d) Artemisinin

11. **Give the source of the following:**
    a) Quinine
    b) Monensin
    c) Salinomycin
    d) Narasin
    e) Maduramicin
    f) Semduramicin
    g) Lasalocid
    h) Artemisin

12. **Matching (Parallel pairs)/Multiple choice (Right choices):**
    a) Broad spectrum avian anticoccidial: Clopidol/Quinolones/Decoquinate/Methyl benzoquate
    b) Most potent anticoccidial ionophore: Maduramicin
    c) Least toxic ionophore aticoccidial: Lasalocid
    d) Anticoccidial ionophore: Monensin/Lasolocid/Maduramicin/Salinomycin/Narasin/Semduramicin
    e) Amprolium: Antithiamine anticoccidial/Reversible B1 deficiency in host/Feed additive anticoccidial in poultry/Suppresses sexual cycle/Gametogony
    f) Avian cocciocidal: Polyether antibiotics/Dinitolmide/
    g) Caecal anticoccidial: Amprolium
    h) Intestinal anticoccidial: Sulfonamides/Ethopabate/Diaminopyrimidines
    i) Caecal and intestinal anticoccidial: Nicarbazin
    j) Arprinocid: Purine analog anticoccidial/Broad spectrum anticoccidial/Blocks hypoxanthnine uptake by coccidia.
    k) Coccidostat: Clopidol/Quinolones/Sulfonamides/Amprolium
    l) Coccidiocidal: Ionophores/Toltazuril/Dinitolmide
    m) Broad spectrum avian anticoccidial: Arprinocid/Halofuginone
    n) Both curative and prophylactic avian anticoccidial: Sulfonamides/Sulfaquinoxaline+Ormetoprim/ Amprolium/Ionophores/Tetracyclines (OTC and CTC)
    o) Prophylactic avian anticoccidials: Clopidol/Decoquinate/Methyl benzoquate/Robenidine/Dinitolmide/ Nicarbazin/Arprinocid/Halofuginone
    p) Anticoccidial sulfonamide: Sulfamethazine/Sulfadimidine/Sulfaquinoxaline/Sulfachloropyrazine/ Sulfadimethoxine
    q) Anticoccidial in bovines: Decoquinate/Amprolium/Sulfamethazine/Monensin/Sulfaquinolxaline/ Diiodohydroxyquinoline/Nitrofurazone
    r) Preventive ovine/caprine anticoccidial: Sulfaguanidine/Monensin/Lasalocid
    s) Curative ovine/caprine anticoccidial: Amprolium/Sulfamethazine/Monensin/Nitrofurazone
    t) Rabbit anticoccidial: Sulfachloropyrazine/Sulfaquinoxaline/Sulfadimethoxine
    u) Canine anticoccidial: Amprolium (Preventive)/Sulfadimethoxine (Curative)
    v) Antibabesial: Phenamidine/Diminazene/Phenazone/Imidocarb/Amicarbalide/Quinuronium/ Acriflavin
    w) Antheilerial: Oxytetracycline/Rolitetracycline/Menoctone/Paravaquone/Bupervaquone/Halofuginone
    x) Halofuginone: Anticoccidial/Antitheilerial
    y) Trypanocidal: Phenamidine/Stilbamide/Diminazene/Homidium/Isometamidium/Antricide prosalt/ Quinapyramines/Suramin/Antimony potassium tartrate/Anthiomaline
    z) Diminazene aceturate: Badesicidal/Trypanocidal/Bactericidal
    aa) Imidocarb propionate: Babesicidal/Antianaplasmic
    bb) Antimilarial blood schizonticidal: Quinine/Chloroquine/Mefloquine/Sulfonamides/Sulfones/ Tetracycline/Doxycycline/Primaquine/Artemisinin/Halofantrine
    cc) Antimalarial tissue schizonticidal: Primaquine
    dd) Antimalarial drug interfering with entry of merozites from liver into RBC: Chloroquine/ Pyrimethamine/Proguanil/Mefloquine/Sulfodoxine/Sulfamethoxypyridazine/Doxycycline
    ee) Antimalarial gametocide: Primaquine/Proguanil/Pyrimethamine
    ff) Antihistomonials: Carbasone/Aminonitrothiazole/Nithiazide/Nitroimidazoles/Dimetridazole/Iporonidazole/ Ronidazole
    gg) Metronidazole effective in: Giardiasis/Trichomoniasis/Amoebiasis/Balantidosis/Amoebiasis
    hh) Quinacrine: Giardiasis
    ii) Radical cure of malaria: Primaquine
    jj) Derivative of artemisinin: Artemether/Artesunate
    kk) Chloroquine: Antimalarial/Anti-inflammatory/Antihistaminic/Local anaesthetic/Antiarrhythmic/ Antigiardial/Antiamoebic

13. **Give the most appropriate reason/explanation for each of the following statements:**
    a) Anticoccidials are almost universally used in broilers.
    b) Use of anticoccidials in layer or breeder birds is not as universal as that of broilers.
    c) Prophylactic approach is better than therapeutic approach in the control of coccidiosis in poultry.
    d) Clopidol/Quinolones have very poor or negligible therapeutic value in avian coccidiosis.

e) Clopidol/Decoquinate/Methyl benzoquate act as coccidostats.
f) Polyether antibiotics/Ionophores are cocciocidal.
g) Monensin and tiamulin should not be concurrently administered to poultry.
h) Robenidone must be withdrawn five days prior to slaughter of poultry birds.
i) Combinatuon of sulfaquinoxaline and ormetropim has synergistic anticoccidial action.
j) Sulfonamide or ethopabate along with amprolium has better anticoccidial efficacy in poultry.
k) Cholinergic drugs should not be administered to quinuronium treated animals.
l) Combination of sulfate and chloride salts of quinapyramine is a better trypanocidal than individual salt.
m) Primaquine is indicated for radical cure of malaria.
n) The artemisinin derivatives artemether and artesunate differ from each other.
o) Tick control measures minimize outbreaks of theileriosis.
p) Metronidazole is a broad spectrum antiprotozoal drug.
q) Quinunonium causes cholinergic signs.
r) Tetracyclines have a very wide chemotherapeutic value
s) Sulfonamides have a wide chemotherapeutic range.
t) Anticoccidial activity of amprolium is neutralized by thiamine dietary supplementation.
u) Amprolium is combined with sulfonamide/ethopabate.
v) Quinapyramine sulfate has curative value only in trypanosomiasis in animals.
w) Quinapyramine chloride is of prophylactic value in trypanosomiasis in animals.
x) Antrycide prosalt has both curative as well as prophylactic value in trypanosomiasis.

What do you mean by Ectoparasiticide & Give in detail about disinfectants.
Write on detail types & mechanism of action of Ectoparasiticide

# Chapter 41: ECTOPARASITICIDES

These are agents used to control or eradicate insect pests (arthropod parasites viz. lice, mites, flies, ticks etc) which parasitisize the body surface of the animals (ectoparasites). These insects also serve as vectors of diseases (for both man and animals). The ectoparasiticides are a class of insecticides.

**Classification of Insecticides Based on Mode of Access into the Insect's Body:**

i) **Contact poison**: Exerts insecticidal action through contact. Insecticide is applied over the body surface of the animals which gets selectively absorbed into the insect's body through its chitinous cuticle (covering) following surface contact.
ii) **Stomach poison**: Absorption of eaten insecticide (as tissues /fat) into insect's body through the membrane in the mid- gut of the insect.
iii) **Systemic poison**: The insecticides are either absorbed through animal's skin or stomach, and then distributed throughout the body.
iv) **Fumigants**: The insecticide is released in the air as gas or suspension and it enters into the insect's body through respiratory system.

**Classification of Insecticides Based on Chemical Nature:**

i) **Organochlorines**: Chlorinated ethanes (DDT, methoxychlor), cyclodienes (Heptachlor, toxaphene, chlordane, dieldrin, endrin etc) and hexachlocyclohexanes (Gamma BHC, lindane etc).
ii) **Organic Phosphates**: Esters of phosphoric group or its thio analog: Dichlorvos, coumaphos, haloxon, diazinon, fenthion, malathion, trichlorfon, famphur etc.
iii) **Carbamates**: Carbaryl and propoxur.
iv) **Pyrethroids**: Allethrin, permethrin, cypermethrin, deltamethrin, flumethrin, fenvalerate, fluvalinate etc.
v) **Macrocyclic Lactones**: Avermectins (Abamectins, doramectin, ivermectin and selamectin) and Milbemycins (Moxidectin and milbemycin oxime)
vi) **Chloronicotinyls** (Imidacloprid, chlorinated derivative of nicotine) and **Spinosyns** (Spinosad).
vii) **Formamidines**: Amitraz.
viii) **Insect Growth Modifiers**: Benzylphenylureas (Diflubenzurin, flufenouron and fluazuron), triazine derivatives (Cyromazine,), pyrimidine derivative (dicyclanil) and juvenile hormone analog (Methoprene).

**Mode of Insecticidal Action:**

**Organochlorines**: Most of these are withdrawn from usage because of their nonbiodegradable nature; environmental persistence and associated health hazards in man, animals and birds (cumulative nature/biomagnification). However, lindane and methoxychlor are used topically because of their relative safety and efficacy. The organochlorines are nervous poisons (neurotoxicity due to high lipid solubility); act by prolonging the depolarization phase (delayed closure of Na+ channels) resulting in repetitive discharge and over excitability of the motor nerves and/or by antagonizing the actions of inhibitory transmitter GABA in the insects. Hyperexcitability is followed by paralysis of the insect (knockdown effect).

**Organophosphates**: These compounds are acutely more toxic and have less environmental persistence as compared to organochlorines; act by irreversibly inhibiting the action of AChE at cholinergic synapses and at the muscle end plates. This results in accumulation of ACh at the postsynaptic membrane leading to neuromuscular paralysis.

**Carbamates**: These also act act as antiChEs like organic phosphates, but cause reversible inhibition of the enzyme.

**Pyrethroids**: The synthetic pyrethroids are very much popular as ectoparasiticides because of their selective toxicity to insects (relatively) and are generally safe in mammals and birds. Further, these are highly biodegradable. But, these are highly toxic to fishes. Pyrethroid compounds interfere with sodium channel present in the axonal membrane of the parasite neuron, causing delayed repolarisation and paralysis of the insect (like organochlorines).

**Macrocyclic lactones**: Avermectins are the fermented products of *Streptomyces avermitilis*; Milbemycins are the products of: *Streptomyces cyanogriseus*. These compounds are effective against a wide range of nematodes and arthropods and as such referred as endectocides. The macrocyclic lactones act by increasing the release of inhibitory neurotransmitter GABA from nerve endings and its binding to its receptors. This leads to increase chloride ion conductance into the nerve cells and hyperpolarization. Recently it has been proposed that ivermectin increases the chloride conductance by acting on a glutamate-gated chloride channel receptor.

**Amitraz** is used against mites, lice and ticks in domesticated animals as spray or dip. It is relatively safe in mammals, but contraindicated in horses. In insects, monoaminooxidase (MAO) is involved in amine neurotransmitters metabolism and octopamine causes tonic contractions of muscles. Amitraz acts by inhibiting MAO and as agonist of octopamine receptors.

**Chloronicotinyls and spinosyns**: Imidacloprid is chlorinated derivative of nicotine and Spinosad is the fermentation product of a soil actinomycetes *Saccharopolyspora spinosa*. These act by interfering with cholinergic transmission in insects (paralysis and death) by binding to nACh receptors.

All the above classes of insecticides exert knockdown effect (rapid kill) on the insect parasites.

**Insect growth modifiers**: These chemicals do not kill the insect parasite directly, but interfere with the growth and development of immature stages: Insect development inhibitors. The benzylphenylureas inhibit chitin formation in cuticle of insects. Triazine and pyrimidine derivatives interfere with deposition of chitin into the cuticle, but not its synthesis. Methoprene, being analog to insect's juvenile hormones, antagonizes their action in metamorphosis of larval stages to adult insect.

**Piperonyl butoxide** is synergistic with knockdown insecticides, especially synthetic pyrethroids. It inhibits the microsomal enzyme system of arthropods and prevents inactivation of the insecticides.

**Application of Ectoparasiticides**: Most of the insecticides are applied topically (as dips, sprays, pour-ons, dusting powders and impregnated devices such as ear tags, bands, collars etc), but some are also applied systemically (to produce systemic effect after reaching into systemic circulation) depending upon the insecticide, target parasite and the host. Pour-ons or spot –ons contain high concentrations and they are either absorbed through the skin and act systemically or act by surface contact. Dips are used for the control of mites, tick, lice and flies in sheep, cattle, goat and horse. The insecticide solutions are also used as shower to the animal. Aqueous emulsion or suspension of insecticides is directly sprayed on the animal body or in cattle shed, barns, stables, dairies etc.

| Insecticide | Animal | Method of Usage | Efficacy Against |
|---|---|---|---|
| **Organochlorines**: | | | |
| DDT | Dog/Cat | 0.2 % Bath or 5% Dust | Ticks, fleas and lice |
| γ BHC | Dog | 0.2 % Bath | Ticks, fleas and lice |
| | Cat/Pup | 0.2% Cream | Ticks and fleas |
| | Pup | 0.5% Dust | Ticks, fleas and lice |
| | Sheep | 0.06% Spray/Dip | Mange, mite and scab |
| | Cattle | 0.05-0.5% Spray | Lice, flies and ticks |
| | | 1% Dust, 0.03-0.05% Dip | Lice |
| Metrhoxychlor | Cattle | 0.025-0.05% Spray | Ticks |
| | | 0.5% Spray | Flies and lice |
| Toxaphene | Cattle | 5% Dust | Ticks |
| | Sheep | 0.25-0.5% Spray | Flies and lice |
| | | 0.5% Dip | Ticks, Scab and mites |

| | | | |
|---|---|---|---|
| **Organic Phosphates:** | | | |
| Coumaphos | Cattle | 0.05% Spray | Lice and fleas |
| | | 0.125-0.25% Spray | Ticks |
| | | 0.25% Spray/Dip | Grubs |
| | | 4% Pour-on | Grubs |
| | Sheep | 0.06% Spray | Lice |
| | | 0.125% Spray | Ked and screwworm |
| Dichlorvos | Dog | 8.9% Collar | Ticks and fleas |
| | Cattle | 1% Dust | Stable flies |
| Malathion | Sheep | 0.5% Spray | Lice and ked |
| | Cattle | 0.5% Spray | Lice, flies and ticks |
| | | 4-5% Dust | Lice and ked |
| | | | Lice, flies and ticks |
| | | | Lice, flies and ticks |
| **Carbamates:** | | | |
| Carbaryl | Dog | 8.5% Collar | Ticks and fleas |
| **Pyrethtoids:** | | | |
| Cypermethrin | Cattle and Sheep | 0.01-0.02% Spray | Ticks |
| | Sheep | 0.005-0.01% Dip | Lice, ked and scab |
| Deltamethrin | Sheep | 1% Dust | Lice |
| Fenvalerate | Cattle and Sheep | 0.05-0.1% Spray | Ticks |
| Permethrin | Cattle and Sheep | 0.02-0.05% Spray | Lice |
| | | 0.1% Spray | Flies |
| | | 0.2% Spray | Ticks |
| Pyrethrins + Piperonyl Butoxide | Dog and Cat | 0.06-0.48% Dust | Fleas, ticks and lice |
| **Amitraz** | Dog | 0.025% Dust | Ticks, lice and mites |
| | Sheep and Cattle | 0.05-0.1% Spry | Ticks, lice and mites |
| **Ivermectin** | Dog | 1% solution 0.2 mg/kg SC | Mange mites |
| | Sheep | 0.08% solution 0.2 mg/kg oral | *Oestrus ovis* and mites |
| | | 1% solution 0.2 mg/kg SC | Nasal bots and mites |
| | Cattle | 1% solution 0.2 mg/kg SC | All ectoparasities |
| | | 1% solution 0.2 mg/kg oral | Grubs and lice |
| | | 0.5% solution 0.2 mg/kg pour-on | Lice, mites and ticks |
| | | 1% solution 0.2 mg/kg SC | Mites |
| **Rotenone** | Dog and Cat | 0.75% Dust | Fleas, ticks and lice |

**Natural Insecticides/Repellants (Botanical Insecticides)**: Nicotine is the alkaloid of leaves of *Nicotiana tabacum*. Rotenone is obtained from powdered root of *Derris eclipta*. Pyrethrum is the powder of flowers heads of *Chrysanthemum cinerariaefolium*. Azadirachtin is the insecticidal principle of neem oil obtained from seeds of *Azadirachta indica*. Garlic oil is obtained from *Allium sativum*. Curcumin is obtained from the rhizomes of *Curcuma longa*. The other natural insect repellents are cinerins, jasmolins, citronella, indalone. Insect attractors (insect pheromone trocosene) help in attracting the insects to a particular site, where they can be killed by application of insecticides.

EXERCISE

1. Classify insecticides used as ectoparasiticides in livestock. Dicuss mode of insecticidal action of each class.

2. **Write a short note on the following**:
   a) Mechanisms of insecticidal action
   b) Synthetic pyrethroids
   c) Organochlorine insecticides
   d) Organic phosphate insecticides
   e) Carbamates
   f) Natural insecticides
   g) Avermectins as insecticides
   h) Macrocyclic lactone insecticides
   i) Application of insecticides for ectoparasite control in livestock, poultry and dogs

3. **Differentiate between the following**:
   a) Organochlorines and Organic phosphates
   b) Chlorinated ethane derivatives and Cyclodienes
   c) DDT and BHC
   d) Organic phosphates and carbamates
   e) Dichlorvos and Propoxur

4. **Explain the mode of insecticidal action of the following ectoparasiticides**:
   a) DDT
   b) BHC/Lindane
   c) Toxaphene
   d) Coumaphos
   c) Propoxur
   f) Deltamethrin
   g) Ivermectin
   h) Amitraz
   i) Spinosad

5. **What do you mean by the following terms? Answer in one or two sentences for each**:
   a) Contact poison
   b) Stomach poison
   c) Systemic poison
   d) Fumigant
   e) Pheromone
   f) Knockdown
   g) Piperonyl butoxide
   h) Chitin inhibitor
   i) Metamorphosis blocker

6. **Give the source of the following**:
   a) Nicotine
   b) Rotenone
   c) Pyrethrum
   d) Azadirachtin
   e) Curcumin
   f) Garlic oil
   g) Avermectins
   h) Milbemycins
   i) Spinosad

7. **What treatment you suggest for treatment of following ectoparasite infestation? Mention the insecticide, its concentration and method of application**:
   a) Ticks in a cow/dog/poultry
   b) Fleas in a dog
   c) Lice in a sheep/hen
   d) Nasal bots in a sheep
   e) Scabies in a sheep
   f) Mange in a dog

8. **Write in brief the value of the following in veterinary practice**:
   a) Avermectins
   b) Organophosphates
   c) Organochlorines
   d) Carbamates
   e) Synthetic pyrethroids
   f) Insect growth regulators

9. **Matching** (Parallel pairs)/**Multiple choice** (Right choices):
   a) Organochlorine: DDT/Methoxychlor/Toxaphene/Lindane/BHC
   b) Organophosphate: Dichlorvos/Haloxon/Fenthion/Trichlorfon
   c) Pyrethroid: Deltamethrin/Fenvalerate/Cyypermethrin/Fluvaginate/Cypermethrin
   d) Carbamate: Carbaryl/Propoxur
   e) Milbemycin: Moxidectin
   f) Chlordane: GABA antagonism
   g) Avermectins: *Streptomyces avermitilis*
   h) Milbemycins: *Streptomyces cyanogriseus*
   i) Spinosad: *Saccharopolspora spinosa*
   j) Pyrethrum: *Chrysanthemum cinarariaefolium*
   k) Rotenone: *Derris eclipta*
   l) Neem oil: Azadirachta indica
   m) Garlic oil: *Allivum sativum*
   n) Macrocyclic lactone: Ivermectin/Doremectin
   o) Dichlorvos: Irreversible AchE inhibition
   p) Carbaryl: Reversible AchE inhibition
   q) DDT: Prolong opening of nerve Na channels
   r) Lindane: Inhibition of dependent-Cl influx
   s) Pyrethroids: Delayed nerve repolarization
   t) Insect pheromone: Tricosene
   u) Ivermectin: GABA potentiation/Glutamate-gated Cl channel facilitation (in insects)
   v) Amitraz: Inhibition of MAO/Octopamine agonist
   w) Imidacloprid/Spinosad: nACh receptor agonist
   x) Triazine/Cyromazine/Pyrimidine derivative (Dicyclanil): Inhibit chitin deposition in cuticle
   y) Benzylphenylureas/Diflubenzuron/Fluazon: Chitin synthesis inhibitor
   z) Methoprene (juvenile hormone analog): Prevents metamorphosis to adult
   aa) Piperonyl butoxide: Potentiator of pyrethroids/Prevents microsomal oxidation of pyrethroids.
   bb) Natural insect repellants: Cinerins/Pyrethrins/Jasmolins/Citronella/Indalone/Garlic oil/Neem oil/Azadirachtin/Curcumin/Rotenone/Nicotine

# Chapter 42: INDIGENOUS DRUGS

Indigenous drugs refer to pharmacologically active principles obtained from the natural products, primarily from the medicinal plants, with proven therapeutic value. The pharmacologically active principles of medicinal plants include alkaloids, glycosides, tannins, resins, fixed oils, volatile oils, oleoresins and gums (See Sources of Drugs: Vegetable drugs).

## POPULAR INDIAN MEDICINAL PLANS WITH PROVEN PHARMACOLOGICAL ACTIVITY

| Botanical Name | Hindi Name | Active Principle | Part (s) Used | Pharmacological Activity |
|---|---|---|---|---|
| *Acacia catechu* | Katha | Tannins: Catechin | Dried bark | Antiseptic/astringent/antidysenteric |
| *Achyranthes aspera* | Apang Chirchira | Triterpinoid saponins | Dried whole plant | Astringent/emetic/oestrogenic/ hypoglycaemic/antiasthmatic |
| *Acorus calamus* | Bach | Sesquiter-penes | Dried rhizome | Stomachic/carminative/antibacterial/ antiinflammatory |
| *Adhatoda vasica* | Vasaka Adulsa Vasa | Alkaloid: Vasicine/ adhatonine | Fresh or dried leaves | Bronchodilator/expectorant/ antitussive/antimicrobial/ abortifacient/ antiinflammatory |
| *Aegle marmelos* | Bel | Coumarins: Marmesin/ marmeline | dried fruit pulp | Antifungal/antidiarrhoeal/anti-dysenteric/antiulcer/antiviral (Ranikhet)/ anthelmintic |
| *Aloe barbadensis* | Musabhar Ghikanvar | Glycoside Aloin/ emodin/aloesin | Dried leaf juice | Immunomodulatoy/woundhealing/antiviral/ analgesic/antiinflammatory/purgative |
| *Andrographis paniculata* | Kirayat Kalmegh | Lactones/ glycosides/ flavonols | Dried aerial parts | Hepatoprotective/immunomodulator/ antiallergic/antipyretic/antithrombotic/ Ca channel blocker |
| *Azadirachta indica* | Neem | Azadirachtin Azadirone Azadiradione Nimbidinin | All parts (dried) Seed oil | Insecticidal/antiinflammatory/antiulcer/ anthelmintic/antibacterial/antifungal/ antiviral/ spermicidal |
| *Berberis aristata* | Rasaut | Alkaloid: Berberine | Dried root | Antipyretic/antiinflammatory/sedation/ antiamoebic/antimuscarinic/cardiotonic |
| *Bacopa monnieri* | Brahmi | Glycosides/ Saponins | Dried leaves/ stem | Brain tonic/antioxidant/antiulcer/ analgesic/spasmolytic/cognitive/ anticonvulsant |
| *Boerhavia diffusa* | Punarnava Gadapurna | Glycoside: Purannavoside | Dried whole plant | Hepatoprotective/diuretic/antifibrinolytic/ Ca channel antagonist/antimicrobial/ immunomodulator/antiinflammatory/ antiviral/antiChE/anticonvulsant |
| *Butea frondosa B.monosperma* | Palas | Monospermine Palasonin | Dried seeds | Anthelmintic/Antifertility |
| *Capsicum annum* | Lalmirchi | Capsaicin | Dried seeds | Anticancer/rubifacient/stomachic/ carminative/antiinflammatory |
| *Carica papaya* | Papita | Alkaloid: Carpaine | Raw/ripe fruit | Antifungal/antiinflammatory/anthelmintic/ antitumor/cardiac depressant/abortifacient |

| | | | | |
|---|---|---|---|---|
| *Cassia fistula* | Amaltas Bahava | Glycoside: Rhein Sennosides A/B | Dried fruit/ pod | Catharatic/antipyretic/antibacterial/ antifungal/anthelmintic/diuretic |
| *Cedrus deodara* | Deodar | Oleoresin Deodarone | Dried bark | Astringent/antibacterial/antifungal/ antipyretic/ antiinflammatory |
| *Celastrus paniculatus* | Malkangni Jyotishmati | Sesquiterpene polyesters, alkaloids, phenolic terpinoids | Dried Fruit/ seed | Tranquilizer/sedative/anticonvulsant/ enhances memory/congnitive/antioxidant/ hypolipidaemic |
| *Centella asiatica* | Brahma manduki | Saponins | Dried Aerial Parts | Brain tonic/sedative/antihypertensive/ antiviral/wound healing/antibacterial/ antioxidant/antifilarial/ /antigiardial/ immunostimulant |
| *Commiphora wighti/mukul* | Guggulu Guggal | Guggulsterones Oleogumresin | Secretion | Antiinflammatory/hypolipidaemic/ Antiobesity |
| *Coriandrum Sativum* | Dhania | Essential oil | Dried Fruits | Carminative/hypolipidemic/microbicidal/ prevents lead deposition/insulin release |
| *Crataeva nurvala c. religiosa* | Barun Varuna | Triterpinoid Alkaloids | Dried stem bark | Antibacterial/hepatoprotective/antifertility/ antiinflammatory/antiurolithiatic |
| *Curcuma longa* | Haldi | Curcuminoids Curcumin | Dried rhizome | Antiinflammatory/stomachic/tonic/ antitumor/hepatoprotective/antiulcer/ hypolipidemic/neuroprotective/antioxidant/ antiandrogenic/antimicrobial/tyrosinase inhibitor/antiarthritic/choleretic |
| *Cyperus rotundus* | Moothoo | Scabequinone Scabequinol Remerin Rotundene | Dried root and tubers | Antiinflammatory/diuretic/anthelmintic/ antidiarrhoeal/galactagogue/tranquilizer/ antipyretic |
| *Datura stramonium* | Dhatura | Hyoscyamine Hyoscine | Dried leaves | Anthelmintic/antispasmodic/insect repellant/ectoparasiticidal |
| *Eclipta alba E.prostrata* | Bhangra | Lactones | Dried whole plant | Antiviral/analgesic/antiinflammatory/ bronchodilator/antibacterial/ 5-lipoxygenase inhibitor/hepatoprotective |
| *Embelia basal E.viridifolia E.ribes* | Baberang | Embelin | Dried fruit | Contraceptive (prevents implantation of fertilized ovum)/anthelmintic/sexual debility in males |
| *Emblica officinalis* | Amla Amlaka | Vitamin C Tannins Alkaloids | Dried fruit | Antacid/hepatoprotective/antioxidant/ Antimicrobial/anticancer/antimutagenic |
| *Ficus racemosa* | Gular | Tannins | Dried bark | Antiulcer/antidiabtic/astringent/tocolytic |
| *Glycyrrhiza glabra* | Jathimadh | Glycyrrhizin | Dried stem | Antiinflammatory/antiulcer/expectorant/ hepatoprotective/estrogenic/antioxidant/ antimicrobial/anxiolytic |
| *Holarrhena antidysenterica* | Karchi Kutaja | Holantosines Holarosine | Stem bark | Astringent/antidysenteric/antiprotozoal/ antibacterial/anthelmintic/antipyretic |
| *Hypericum perforatum* | | Hypericin | All parts | Germicidal/antiinflammatory/MAO inhibitor/ photodynamic (primary) |

| | | | | |
|---|---|---|---|---|
| *Lawsonia innernis* | Mendhi | | Dried leaves | Antinflammatory/antimicrobial/wound healing/analgesic |
| *Mentha piperata* | Pudina | Menthol Menthone | Fresh leaves | Carminative/spasmolytic/antiallergic/ antiulcerogenic/antibacterial/cholagogue/ antiinflammatory/diuretic/sedative |
| *Momordica charantia* | Kareli | | Ripe fruit Seeds (dried) | Antidiabetic/antigout/laxative/ectopara-siticide/antibacterial/hepatoprotective |
| *Moringa oleifera* | Shajna Munaga | Glycosides | Leaves Fruit | Antibacterial/antiinflammatory/hepatoprotective/ CNS depressan/antispasmodic/wound healing |
| *Murraya koenigii* | Karipatta/ curry leaves | Alkaloids Curryanine Koenine | Leaves | Cardiotonic/tonic/stomachic/antiemetic/ antipyretic/laxative |
| *Musa paradisiaca* | Kela | | Fruit | Antibacterial/styptic/antidiabetic/laxative |
| *Ocimum sanctum* | Tulsi | Volatile oil: Euganol and beta-caryophyllene | Leaves | Antiinflammatory/hypoglycaemic/immuno-modulator/antistress/analgesic/antipyretic/ anticulcer/antihypertensive/CNS depression/antioxidant/antitumor/antibacterial |
| *Phyllanthus amarus* | Bhuiavla | Lignans and Tannins | Tender aerial parts | Hepatoprotective/antidiarrhoeal/ anticancer/antimutagenic/contraceptive |
| *Phyllanthus niruri* | Jarmala | Lignans and Tannins | Whole plant | Hepatoprotective /astringent/antibacterial/ diuretic |
| *Picrorhiza kurroa* | Kutki Kuru | Glycosides | Dried rhizome | Hepatoprotective/immunostimulant/ choleretic/antiasthmatic/antidiabetic/ antioxidant/antiulcer/antileishmaniasis |
| *Piper betle* | Pan | | Fresh leaves | Antiinflammatory/antibacterial/carminative/ analgesic/anti sore-throat/anthelmintic |
| *Piper cubera* | Kababchini | Lignan: Cubebin | Dried fruit | Antitussive/antibacterial/antiinfluenza/ expectorant |
| *Piper longum* | Pipli | Alkaloid: Piperine | Dried Fruiting Spikes | Antiallergic/antiasthmatic/hepatoprotective/ anthelmintic/antiamoebic/cholagogue/ analgesic/sedative/carminative/ abortifacient |
| *Piper nigrum* | Kalimirch | Alkaloid: Piperine | Dried unripe fruit | **Bioenhancer**/Anticonvulsant/antiallergic/ antipyretic/analgesic/antioxidant/hepatopro-tective |
| *Plantago ovata* | Isabgol | Mucilage poly-Saccharide | Dried seeds | Bulk forming laxative/immunostimulant/ antihypercholesterolemic |
| *Podophyllum hexandrum* | Papra | Podophyllotoxin | Dried rhizome and root | Antitumor/radioprotective/antifungal/antiviral |
| *Rauwolfia serpentina* | Sarpagandh | Alkaloids: Reserpine and Rescinnamine | Dried root | Antihypertensive/tranquilizer/neurosedative |
| *Ricinus communis* | Arand | Ricinoleic acid Ricin Castor oil | Leaves, root seeds | Hepatoprotective/antitympanitic/infertility/ antitumor/antimicrobial/nematicidal/purgative |

| | | | | |
|---|---|---|---|---|
| *Sida cordifolia* | Bala/Bariar | Phytosterol | Dried Root | Antibacterial/antifungal/antiinflammatory/ analgesic/hypoglycaemic/adaptogenic/ immunostimulant |
| *Solanum americanum S.ngrum* | Makoi Kakmachi | Alkaloids: Solanine and solasodine; Glycosides: Solasonin and Solamargin | Dry aerial parts | Hepatoprotective/expectorant/ antiinflammatory |
| *Solanum xanthocarpum* | Kateli | Alkaloid: Solasodine | Dried whole plant | Antispermatogenic/anticancer/antidiabetic/ antiasthamatic/analgesic/cytoprotective |
| *Swertia chirata* | Chiryata | Amarogentin Amaroswerin | Dried whole plant | Antiinflammatory/hepatoprotective/ anticancer/immunostimulant/hepatoprotective/ antiulcerogenic/antiChE/CNS depressant/ antimalarial/antioxidant/α-glycosidase inhibitor/ antileishmanial |
| *Syzygium aromaticum* | Laung Lavang | Volatile oil: Eugenol/ β-caryopyhllene | Dried flower buds | Antiherpisvirual/antibacterial/ antithrombotic/antioxidant/carminative/ stomachic/antiulcer |
| *Terminalia belerica* | Behera | Tannins | Pericarp of dried fruit | Hypolipidemic/expectorant/laxative/ cholagogue/antimicrobial/diuretic |
| *Terminalia chebula* | Harad Harahra | Tannins | Dried fruit | Laxative/astringent/hypolipidemic/ antioxidant/hepatoprotective/adaptogenic/ antibacterial/antiviral |
| *Tinospora cordifolia* | Giloe Guduchi | Diterpenes, alkaloids and a glycoside | Dried Stem | Anticancer/antiulcer/antipyretic/antioxidant/ immunostimulant/hypolipidemic/cardiotonic/ analgesic/hepatoprotective |
| *Tribulus terrestri* | Gokhru | Saponins and Alkaloids | Dried fruit | Diuretic/antiurolithiatic/renoprotective/cardiac stimulant/cytoprotective |
| *Veronia anthelmintica* | Somraj | Sitosterols | Dried seeds | Anthelmintic/diuretic |
| *Withania somnifera* | Asvagandh | Withanolides and alkaloids | Dried root | Antistress/adoptogenic/immunostimulant/ anticancer/anthelmintic/anticonvulsive/ antibacterial/antioxidant/antidepressant |
| *Zingiber officinale* | Adrak Sunth | Oleoresin Volatile oil | Rhizome (fresh or dry) | Antioxidant/antiallergic/carminative/anti-emetic/antiinflammatory/thromoboxane synthesis inhibitor/prevents platelet aggregation (increases bleeding time) |

## EXERCISE

1. Name any two most commonly used indigenous medicinal plants for the following indications:

a) Antibacterials/Antiseptics
b) Antinflammatory
c) Wound healing
d) Anthelmintics
e) Antifungals
f) Antidiarrhoeals
g) Hepatotonics
h) Immunostimulants
i) Antacids
j) Ectoparasiticides
k) Galactagogues
l) Digestives
m) Carminatives

# SECTION VI : TOXICOLOGY

## CHAPTER – 43: GENERAL TOXICOLOGY

### 1. Historical Background

The earliest record of poisons is in Egyptian Kahun Papyrus (2000 BC) and Ebers Papyrus (1550 BC), which mentioned poisons of plant origin like aconite and opium. The Hippocratic School of Physicians (460-375) recognized the metallic poisons such as antimony, copper, lead, mercury etc. They also suggested emesis in preventing absorption of toxicants. Geber Ibn Hajar (702-765) tried to differentiate drugs and poisons and emphasized that drugs could become poisonous if given in high doses. M.J.B. Orfila (1787-1853), a Spanish Physician introduced toxicology as a separate discipline dealing with poisons. He developed methods for detection of poisons, and is rememebered as 'Father of Toxicology'.

### 2. Scope of Veterinary Toxicology

In modern sense toxicology not only deals with the study of toxicants on the living organisms, but also with harmful effects of any other agent (chemical, physical or biological) on the ecosystem. A modern toxicologist immensely contributes to environmental/life scienes, physiology, pharmacology, pathology, forensic science, clinical medicine, occupational health science, public health etc. A veterinary toxicologist, though directly concerned with studies of adverse effects of drugs or other xenobiotics on the health of animals and birds, indirectly has a significant role in advancement of the sciences mentioned above. In dealing with toxicological aspects, a veterinary toxicologist has a challenging and highly complicated job to face, since he/she has to deal with different species of animals and birds. As in veterinary pharmacology, species variation is the essence of veterinary toxicology. The scope of veterinary toxicology is very vast. A veterinary toxicologist needs to understand the variation in toxicity of different agents in different species of animals, whereas a human toxicologist deals with only one species. Safety evaluation of drugs or other chemicals in animals is incomplete without understanding their toxicology.

It is the general practice to attribute the cause of every unknown disease to some poisoning or toxicity. The grazing livestock are indiscriminate eaters, especially when they are hungry during drought or scarcity periods. Thus they ingest food as well as nonfood materials such as industrial/household wastes, poisonous plants, discarded drugs or any other chemicals. Absence of specific grazing areas or pasture fields confounds the problem of toxicity in animals due to wide distribution of nonfood or toxic plants in the waste lands. Indiscriminate industrialization and intensive plant protection measures in the name of pest control to increase crop yields have greatly contributed to chemical pollution of the environment and indirectly the health of livestock including birds and fishes. Criminal or malicious poisoning is also not uncommon. The grazing livestock, especially under wild conditions, are also at risk of venomous bites or stings. Therefore, the veterinary toxicologist has an enormous task in welfare of animals and birds through prompt diagnosis, treatment and prevention of toxicities in animals.

### 3. Definitions

Toxicology originated from Greek words Toxicon (poison) and Logos (Science) i.e. Science of Poisons.

In modern sense, toxicology refers to study of adverse effects of chemical, biological and physical agents (xenobiotics) on living systems. It is defined as study of sources and nature of toxicants; absorption, distribution, metabolism (toxicokinetics) of toxicants in the animal body; mode of action, biochemical and physiological effects of toxicants on the animal (toxicodynamics) and diagnosis, prevention and treatment of poisoning. Any agent which is capable of impairing normal physiological function may be called as a poison or toxicant.

**Poison** is defined as an agent, either solid, liquid or gas, which when applied to the animal's body outwardly or in any way introduced into it, can destroy life without acting **mechanically** (bullet can kill an animal, but it causes death due to mechanical damage). Toxicant and poisons are synonyms: Any substance that is capable of causing harmful effects (poisoning or toxicity).

**Toxicity** is defined as inherent capacity of an agent to cause adverse reaction, which is expressed in quantitative terms as quantity per unit body weight (mg/kg) to produce a given effect. By such as expression (MLD) different agents are classified (**toxicity potential**) as listed below:

| Class | | Oral Median Lethal Dose (MLD) in rat |
|---|---|---|
| Extremely toxic | : | < 1 mg/kg |
| Highly toxic | : | 1 – 50 mg/kg |
| Moderately toxic | : | 50 – 500 mg/kg |
| Slightly toxic | : | 500 – 5000 mg/kg |
| Practically nontoxic | : | 5 – 15 gm/kg |
| Relatively harmless | : | > 15 gm/kg |

**Hazard** refers to the probability of appearance of an adverse effect due to an agent depending upon its usage pattern. Hazard generally refers to the likelihood of occurrence of toxicity due to a toxicant. **A least toxic compound may be most hazardous** (freely used without any restrictions and hence probability of exposure of living organisms to it and the risk of health hazards are very high: DDT). **A most toxic substance may be least hazardous** (used with extreme caution and hence probability of exposure of living organisms to it and risk of health hazards are very low or nil: Cyanide). Thus, toxicity and hazard may be inversely related.

**Toxins** are poisonous chemical agents produced by living organisms (biotoxins) and include:
Phytotoxins: From plants (abrin, ricin)
Mycotoxins: From molds (aflatoxins)
Zootoxins: From lower animals (ticks and snakes)
Bacterial toxins: From bacteria (tetanus, botulinum)
Venoms are **zootoxins** produced by snakes injected by sting or bite.
**Toxinology**: Study of sources, nature and effects of toxins on man and animals, their prevention and treatment.

The important branches or sister disciplines of toxicology include:
**Environmental Toxicology**: Deals with study of sources and effects of environmental pollutants, including food additives/preservatives/pesticides (residues) on living systems in the environment.
**Occupational Toxicology**: Deals with the study of adverse effects of exposure to harmful chemicals due to occupation (Industrial toxicology) or exposure of farm animals to harmful pesticides during agricultural operations.
**Genetic Toxicology**: Deals with the study of adverse interactions of toxicants on hereditary process or in alteration in genetic makeup: Mutations.
**Wildlife Toxicology**: Study of adverse effects of environmental pollutants on wild animals, including birds.
**Veterinary Toxicology**: Toxicology (see above) in relation to animals and birds.
**Forensic Toxicology**: Deals with medico-legal or vetro-legal aspects of (criminal or malicious) poisoning or intoxication (analytical aspects for confirmative diagnosis to arrive at the actual cause of death).

## 4. Causes or Sources of Poisoning

**1. Natural Sources/Causes:**

A. Toxic/Poisonous plants (Lantana, Datura, Ipomoea, Oleander).
B. Toxic Minerals/Metals (Contamination/accumulation of Hg, Pb, As, nitrates, Se, Oxalates in plants or water).

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M.Vsc-Pathology.

C. Toxic/Poisonous Animals (snakes, scorpions, bees, toads etc)
D. Cosmic Radiation

**2. Man Made Causes/Sources:**

**A.** Malicious Poisoning: Criminal killing of animals (*Abrus, Datura, Calotropis*, Arsenic, Cyanide, Pesticides, Zinc phosphide etc)

**B.** Accidental Poisoning: Indiscriminate use of drugs/pesticides. Accidental ingestion of toxicants due to faulty storage.

**C.** Environmental Pollution: Contamination of herbage and water by environmental pollutants. Radiation hazards (explosion of nuclear weapons, accidents in nuclear reactors, improper disposal of nuclear wastes) and use of chemical warfare weapons/agents.

**D.** Occupational Poisoning: Exposure to harmful chemicals related to occupation.

**5. Classification of Toxicants/Poisons**

A. **Basing on Source or Origin:**
   i. Natural: Toxic plants, minerals/metals and animals (see above)
   ii. Synthetic: Pesticides, dangerous drugs, food additives, industrial effluents/wastes etc

B. **Basing on Effects on Animal's Body :**

   **i. Poisons Causing respiratory Insufficiency:**
   a. By inactivating hemoglobin: Nitrates, CO, chlorate etc.
   b. By interfering with cellular utilization of oxygen: CN, $H_2S$ etc.
   c. By preventing erythropoiesis: Radioactive substances
   d. By interfering with oxygen exchange in pulmonary alveoli : ANTU
   e. By causing lysis of erythrocytes: Haemotoxic snake venoms
   f. By causing haemorrhages: Sweet clover, warfarin

   **ii. Poisons Causing Derangement of Nervous Function:**
   a. Depressants: Barbiturates, chloral hydrate etc.
   b. Stimulants: Strychnine, cocaine, organochlorine insecticides etc.
   c. By damaging brain and spinal cord: Salt, organomercurials etc.
   d. By stimulation and/or depression: AntiChE agents.

   **iii. Poisons Causing Visceral Organ Dysfunction:**
   a. Colic: Acids, alkalis, thallium etc.
   b. Hepatic insufficiency/disease: $CCl_4$, coal tar, aflatoxins etc.
   c. Renal damage/disease: Pb, As, Cd, Oxalates etc.
   d. Gastroenteritis: Mercury, salt etc.
   e. Cardiotoxicity: Oleander, digitalis, calotropis etc.

   **iv. Poisons Causing Lameness:**
   a. Abnormalities in long bones: Fluorine, selenium, copper etc.
   b. Painful lesions on feet: Ergot, fluorine etc.

C. **Basing Chemical Nature:**
   i. Inorganic Toxicants: Metals (Pb, Hg, Cu);nonmetals (nitrites, P, S etc); Acids (HCl, $H_2SO_4$) and Alkalis (KOH)
   ii. Organic Toxicants: Hydrocarbons (benzene), halogen derivatives of hydrocarbons (BHC, DDT); alcohols and phenols (methanol, phenol); alkaloids (strychnine), glycosides (calotropin), proteins (abrin, ricin)

D. **Basing on Physical State:**
   i. Gases: CO, HCN, Phosphine, $SO_2$ etc.
   ii. Liquids: Acids and alcohols
   iii. Solids: Strychnine, atropine, DDT etc.
   iv. Dusts: Asbestos, silicon, and metallic dusts.

E. **Basing on Toxicity Potential:** See above under toxicity: Class and oral MLD in rat.

## 6. Mode of Action of Toxicants

1. **Specific Actions:**
   i. **Receptor-mediated action:** As agonists or antagonists on neurotransmitter receptors (atropine, strychnine, morphine etc.).
   ii. **Enzyme-mediated action:** Fluoroacetate, OP and carbamate insecticides etc.
2. **Non-Specific Actions:**
   i. Physical Toxicants: Physical deposition in tissues/organs: metal dusts, silicon, asbestos in lungs. Pb in bones etc.
   ii. Direct chemical injury: Corrosives, and caustics (acids, alkalis, phenol, alcohols)
   iii. Necrosis of epithelial cells: Oxalates, P, mercury
   iv. Interfering with metabolism:
      **a.** Uncoupling/inhibition oxidative phosphorylation: No ATP formation (arsenates, dinitrophenol, chlorophenol fungicides etc).
      **b.** Inhibition of nucleic acid/protein synthesis: Interfering with DNA transcription and translation (Aflatoxins, organomercurials).
      **c.** Interference with fat metabolism: $CCl_4$, yellow P.
   v. Injury to blood and vascular system: Anti Vitamin K: prevention of formation of prothrombin and factors VII, IX and X (warfarin and sweet clover)
   vi. Interfering with function of ion channels: DDT and pyrethroids.
   vii. Formation of secondary toxic metabolites: Fluoroacetate to fluorocitrate, ammonia from urea etc.
   viii. Immunodeficiency: Reduced antibody formation, interfering with complement and altered neutrophil function (heavy metals, mycotoxins, some drugs etc.
   ix. Teratogenecity: Abnormal fetal development. Plants of *Veratrum* spp., heavy metals and drugs like quinine, thalidomide etc.
   x. Carcinogenecity: Induction of carcinoma/tumors: DDT, oestrogen and saccharin.
   xi. Deficiency of nutrients : Mutual antagonism between Cu and Mb, hypocalcaemia by oxalates
   xii. Deposition in tissues: Fluoride in teeth and bones, Pb in bones, oxalate and sulfonamide crystals in renal tubules etc.

## 7. Toxicokinetics

Toxicokinetics deals with toxicants similar to pharmacokinetics of drugs.

**Metabolism/Biotransformation of xenobiotics:** Compounds that are lipid soluble and unionised are better absorbed and remain in body unless converted to water soluble and polar (ionic) form. The chemical conversion of foreign compounds in the body is done by metabolism. Metabolism results in:

A. Conversion of toxic agent to inactive compound (inactivation/**detoxification**): DDT to DDE/DDA.
B. Conversion of a nontoxic agent to toxic compound (**lethal synthesis**): Malathion to malaxon, Methanol to formaldehyde, phenacetin to paracetamol etc.
C. Conversion of a toxic agent to another toxic compound of different activity (toxic intermediates): Aflatoxin B1 (hepatotoxic) to aflatoxin M1 (carcinogenic)

**Pathways of Biotransformation:**

Phase I: Oxidation, reduction and hydrolysis

Phase II: Conjugation/synthetic reactions: Glucuronidation, sulfation, acetylation, methylation and glutathione conjugation, amino acid conjugation and thiosulfate conjugation. Refer drug metabolism for details.

## 8. Types of Toxicity

**Acute**: Results from exposure to single high doses with immediate onset of toxicity signs and symptoms and may also cause death. Experimental acute toxicity testing is done to find out LD50 (MLD) of drugs or other chemicals. The affected animals may not show significant haematobiochemical or pathological changes due to sudden death.

**Subacute**: Results from exposure to low doses (subtoxic) of an agent repeatedly over a period of 90 days. Toxicity develops gradually where the animals may show reduced feed intake, retarded growth rate, specific haematobiochemical and pathological changes.

**Chronic**: Results from exposure to an agent at very low doses over a long period (> 6 months). Toxicity develops gradually where the animal shows reduced feed intake, retarded growth rate, specific haematobiochemical and pathological changes.

Cumulative toxicants/poisons (DDT, lead etc) have a tendency to accumulate in tissues/organs show subacute or chronic toxicity.

Safety evaluation of any drug or a chemical includes experimental investigation of its acute, subacute and chronic toxicities.

## 9. Factors Modifying Toxicity

Several considerations influence the toxicity of an agent. It is similar to factors modifying drug responses.

### A. Factors Related to the Toxicant:

1. **Nature of the Compound** (Physicochemical properties):
   a. Lipid solubility: High lipid solubility ensures rapid absorption leading to more toxicity (DDT).
   b. Degree of ionization: Rapidly inonizable compounds are highly water-soluble and hence are less toxic (ammonium ion is water soluble and less absorbed than ammonia).
   c. Polarity: Nonpolar compounds are rapidly absorbed than polar compounds and hence are highly toxic than polar compounds.
   d. Molecular weight: Low mol. Wt compounds are rapidly absorbed and more toxic than high mol wt. compounds.
   e. Physical nature: The order of toxicity is Solids < powder (coarsely powdered < finely powdered) < liquids (differences in dissolution or disintegration and solubility and rate of absorption). Gases induce rapid toxicity due rapid absorption through inhalation. In liquid form, the nature of solvent alters toxicity: dermal application of insecticides in water medium may be nontoxic, but becomes toxic in oily medium (kerosene or veg. Oils: rapid absorption, yellow P is highly toxic in oily solution).
   f. Chemical nature: Trivalent arsenicals > toxic than pentavalent arsenicals; barium carbonate is toxic but not barium sulfate, CO > toxic than CO2, methanol > toxic than ethanol.
2. **Dose of the Compound**: Toxicity intensity is directly related to the dose. Drugs in normal dose have beneficial effect, but at high doses become toxic.
3. **Source of the Compound**: In case of toxic plants, seeds or root have higher concentration of toxic principles and are more toxic than other parts. Wildly grown plants are > toxic than cultivated plants (*Acacia leucopholoea*). Faulty storage of feeds also results in higher toxicity (mold infestation of feeds).

### B. Factors Related to the Nature of Exposure:

1. **Frequency of Exposure**: A less acutely toxic cumulative compound becomes toxic after prolonged exposure (cumulative poisons which accumulate in body).
2. **Simultaneous Exposure**: While exposure to 2 or more compounds at the same time, one may alter the toxicity of the other (interaction) which may result in increase in toxicity (potentiation : Increase in pyrethrin toxicity by piperonyl butoxide) or decrease in toxicity (antagonism : Cu and Mb are mutually antagonistic, DDT lowers parathion toxicity).
3. **Route of Exposure**: More toxic by oral route than dermal route. Inhalation is more toxic than oral route (elemental Hg nontoxic by oral route, but highly toxic when its vapour is inhaled). Drugs administered in high doses, especially by parenteral routes, are more toxic than their administration orally.

C. **Factors Related to the Animal:**

1. **Species**: Belladonna or atropine is toxic in all spp. except rabbit (presence atropinase in liver, which inactivates atropine). Red squill is toxic to rats, but not in dogs/cats (which vomit). Phenol is toxic to cat (no glucuronidation) but not in dog. Strychnine toxicity decreases in the order Dog > Poultry > amphibians. Monogastrics are less susceptible (gastric acidity destroys glycosidase liberating HCN) to cyanogenetic plant poisoning as compared to ruminants.
2. **Individual variation**: Some are hypersensitive and some are hyposensitive or resistant to toxicities in a population (normal biological variation/idiosyncracy).
3. **Sex**: Males are more resistant (due to testosterone) than females (testosterone pretreated females also become resistant). Toxicity tests are carried out using both the sexes at each dose level.
4. **Age**: Young stock is more sensitive than the adults (mechanisms of metabolism and/or detoxification and excretion are not fully developed). Old animals are more susceptible than normal adults (the above mechanisms become less effective or defective)
5. **Health Status**: Animals with hepatic or renal insufficiency are more susceptible to toxicities due to impaired detoxification and excretion. Constipation increases (more absorption) and diarrhoea decreases (less absorption) toxicity of an orally ingested toxicant. Animals with dermal wounds suffer from toxicity when sprayed with insecticides for ectoparasitic control (rapid absorption).
6. **Metabolism**: Metabolism usually inactivates a toxicant (detoxification), but sometimes nontoxic compounds become highly toxic after metabolism (lethal synthesis). Examples see under toxicokinetics (metabolism) above.
7. **Size and Weight**: Large sized animals require more dose of a toxicant. Obese/fatty animals can tolerate high doses of fat-soluble toxicant (DDT, barbiturates) than lean or emaciated animals. Ruminants require large oral doses than nonruminants (voluminous rumino-reticular contents dilute or inactivate ingested compounds).
8. **Nutritional Status**: Starved animals are more susceptible (metabolic ineficiency of liver due to depletion of glycogen) to toxicities than well-fed healthy animals. Malnourished or protein deficient animals more sensitive to toxicities (less production of drug metabolising enzymes). Vitamin E and C deficiency enhances tissue damage from free radicals.
9. **Genetic Status**: Thoroughbred animals are more resistant than nondescript breeds. Individuals with glucose-6-phosphate dehydrogenase deficiency are more prone to haemolytic effects of sulfonamides, asprin and acetanilid.

D. **Factors Related to the Environment:**

1. **Temperature**: Low environmental temperature enhances metabolism of xenobiotics (increase in metabolic activity to keep body warm). Dermal toxicity of insecticides increases in hot weather (increased absorption due to more blood supply to periphery to keep the body cool.
2. **Relative humidity**: Dermal absorption of OP insecticides is rapid in hot humid weather conditions.
3. **Atmospheric pressure and Altitude**: Toxicity of CO, barbiturates and cyanide increases in high altitudes due to low oxygen tension. Greater toxicity of red squill, strychnine, digitalis in high altitudes due to low cardiovascular function.
4. **Light**: Photosensitization reaction is more marked in animals exposed to bright sunlight. Eye toxicity of atropine (mydriasis and cycloplegia) is more marked in animals exposed to direct sunlight.
5. **Environmental Pollution**: Chemical pollutants in the environment influence the toxicity due to alteration in metabolism (induction or inhibition of hepatic microsomal enzymes resulting in altered metabolism and excretion of xenobiotics). Noise pollution aggravates convulsive poisons like strychnine (increase in intensity of seizures and hyperesthesia).

## 10. General Principles of Diagnosis and Treatment of Toxicity

Effective treatment of poisoned animals can be adopted only after arriving at proper diagnosis. The Veterinary Clinician must distinguish between poisoning and other disease states. Diagnosis of poisoning in animals may be three types: Tentative, presumptive and confirmative.

**Tentative** diagnosis is first made based on case history and clinical examination of affected animal and observing the gross pathological changes. This helps in elimination of other diseases. Investigations should be made to find out access of animals to the toxicant or its use in their vicinity.

**Presumptive** diagnosis is made based on correct history, characteristic clinical signs and pathological observation in association with the knowledge of access to the suspected toxicant has occurred. Successful use of antidotal therapy supports tentative or presumptive diagnosis.

**Confirmative** diagnosis is made by qualitative and quantitative estimation of the toxicant in feed, water, ruminal contents, blood, urine or animal tissues.

**Line of Treatment of Toxicity Cases:**

**General Procedures:**

1. Shifting to fresh water and feed
2. Removal of unabsorbed toxicant from the body: Washing skin with soap and water in dermal exposure; by emesis, lavage or purgation in oral exposure. Apomorphine and saline purgatives are preferred in small animals. Rumenotomy in ruminants and replace the rumen contents by fresh feed and saline.
3. Relief from respiratory insufficiency: Removal of obstruction in respiratory passages, if any at once.
4. Shifting to quiet quarters.
5. **General Antidotal Therapy**: When nature of toxicant is not known or when there is no specific antidote:
   i. Universal Antidote: 2 parts of powdered charcoal and 1 part of kaolin (adsorb poisons), 1 part of tannic acid (precipitates alkaloidal and metallic poisons) and 1 part of magnesium oxide (causes purgation). Dose: Small animals: 5-50 gm; Large animals: 250-500 gm (Orally).
   ii. Neutralization of acid poisons by dilute alkalis (lime water, powdered chalk or magnesia).
   iii. Mild acids (5% acetic acid or vinegar) neutralize alkali poisons.
   iv. Tr. Iodine (15-20 drops in a glass of water) precipitates alkaloids, Pb and Hg.
6. **Specific Antidotal Therapy**: If actual toxicant is known.Specifically neutralizes the action of toxicants :
   i. Atropine in OP and carbamate insecticide poisoning.
   ii. ChE reactivators (2-PAM) in OP insecticide poisoning.
   iii. Sodium nitrite and sodium thiosulfate in HCN/cyanide poisoning.
   iv. Vitamin K in warfarin and sweet clover toxicity.
   v. Chelating agents like BAL in As and Hg poisoning and dicalcium EDTA in Pb toxicity.
7. **Symptomatic treatment**: Sedatives/hypnotics in nervous excitability (tremors/convulsions); Analeptics in respiratory depression; intestinal astringents in diarrhea; analgesics to relieve pain; cardiac stimulants in failing heart.
8. **Supportive Therapy**: Administration of fluids and electrolytes, liver tonics, corticosteroids, haematonics, digestive stimulants or broad-spectrum antibiotics to suppress secondary bacterial infections.

EXERCISE

1. Give the classification of poisons/toxicants based on their effects on animal's body along with appropriate examples.
2. What do you mean by toxicokinetics? Describe in brief the different processes of absorption of toxicants.
3. What do you mean by toxicodynamics? Describe the mode of action of toxicants.
4. Describe the different factors related to the toxicant that influence the outcome of toxicity.
5. Describe the different animal related factors that influence the outcome of toxicity.
6. Describe the general line of treatment of toxicity in animals.

7. **Write a short note on the following**:
   a) Scope of veterinary toxicology
   b) Causes/Sources of poisoning
   c) Mode of action of toxicants/poisons
   d) Types of toxicity
   e) Diagnosis of poisoning cases
   f) General antidotal therapy
   g) Specific antidotal therapy
   h) Environmental factors influencing toxicity
8. **Differentiate between the following pairs**:
   a) Poison and bullet
   b) Antagonism and potentiation
   c) MLD and MED
   d) Hazard and toxicity
   e) Toxicokinetics and toxicodynamics
   f) Toxin and venom
   g) Emesis and lavage
   h) Phytotoxin and zootoxin
   i) Detoxication and lethal synthesis
   j) Acute toxicity and subacute toxicity
   k) Subacute toxicity and chronic toxicity.
   l) Tentative diagnosis and presumptive diagnosis
   m) Presumptive diagnosis and confirmative diagnosis
   n) General antidotal therapy and specific antidotal therapy
   o) Symptomatic treatment and supportive treatment
   p) Poison and toxin
9. **Explain each of the following with appropriate examples**:
   a) A least toxic compound may be highly hazardous.
   b) A most toxic compound may be least hazardous.
   c) Metabolism determines the outcome of toxicity of a compound.
   d) Antagonism in toxicity.
   e) Potentiation in toxicity.
   f) General antidotal therapy.
   g) Specific antidotal therapy.
   h) Lethal synthesis.
   i) Species variation in toxicity.
   j) Chelating agents and toxicity.
   k) Enzyme inhibition and toxicity.
   l) Antimetabolites and toxicity.
   m) Symptomatic treatment.
   n) Supportive therapy.
   o) Presumptive diagnosis.
   p) Confirmative diagnosis.
   q) Cumulative poison.
10. **What do you mean by the following?/Give the definition of the following**:
   a) Xenobiotic
   b) Zootoxin
   c) Phytotoxin
   d) Venom
   e) Toxicity
   f) Hazard
   g) Poison
   h) Toxicokinetics
   i) Toxicodynamics
   j) Toxinology
   k) Environmental toxicology
   l) Forensic toxicology
   m) Malicious poisoning
   n) Occupational toxicity
   o) Environmental Pollution
   p) Teratogenicity
   q) Mutagenicity
   r) Carcinogenicity
   s) Teratogen
   t) Mutagen
   u) Carcinogen
   v) Acute toxicity
   w) Subacute toxicity
   x) Chronic toxicity
   y) Cumulative poison
   z) Lethal synthesis
   aa) Detoxication
   bb) Specific antidote
   cc) General antidote
   dd) Tentative diagnosis
   ee) Presumptive diagnosis
   ff) Universal antidote
   gg) Supportive treatment
   hh) Symptomatic treatment

11. **Substantiate each of the following statements by giving the most appropriate reason/explanation in one or two sentences:**
    a) Toxicity and hazard may be inversely related.
    b) A least toxic compound may be highly hazardous.
    c) A most toxic compound may be least hazardous.
    d) Metabolism determines the outcome of toxicity of a compound.
    e) Cumulative toxicants cause subacute/chronic toxicity.
    f) Rapidly ionizable compounds are less toxic.
    g) Nonpolar compounds are highly toxic.
    h) Belladonna/Atropine is nontoxic to rabbits.
    i) Strychnine toxicity decreases in the order dog > poultry > amphibians.
    j) Monogastrics are less susceptible to cyanogenic plant poisoning as compared to ruminants.
    k) Constipation increases the toxicity of ingested toxicants.
    l) Diarrhoea decreases the toxicity of ingested toxicants.
    m) Starved animals become highly sensitive to toxicants.
    n) Orfila is regarded as 'father of toxicology'
    o) Toxicity of a compound is enhanced in renal/hepatic disease.
    p) Rumen microflora determines the toxicity of an ingested toxicant.
    q) Universal antidote may be used in any oral intoxication in dog.
    r) In acute toxicity the clinical signs and symptoms are seen immediately.
    s) In subacute/chronic toxicity the clinical signs and symptoms are delayed in onset.
    t) In acute toxicity pathognomonic haemato-pathological alterations are not generally seen.
    u) Toxicity and dose are inversely related.
    v) Very young and old animals are highly sensitive to toxicants.

12. **Matching** (parallel pairs):
    a) Orfila: Father of toxicology
    b) Geber Ibn Hajar: Differentiated toxicant and drug
    c) DDT: Less toxic, but more hazardous
    d) Cyanide: Most toxic, but less hazardous
    e) Abrin: Phytotoxin
    f) Botulinum: Toxin
    g) Venom: Zootoxin
    h) Aflatoxin: Mycotoxin
    i) Botulinum: Bacterial toxin
    j) Carbon tetrachloride: Hepatotoxic
    k) Oleander: Cardiotoxic
    l) Strychnine: Neurotoxic
    m) Teratogenicity: Fetal abnormalities
    n) Carcinigenicity: Tumor formation
    o) Mutagenicity: Alteration in genes
    p) Lethal synthesis: Metabolic activation
    q) Detoxication: metabolic inactivation
    r) Hydrolysis: Phase I reaction
    s) Conjugation: Phase II reaction
    t) DDT: Cumulative toxicant
    u) Ionized compound: Less toxic
    v) Nonpolar compound: Highly toxic
    w) Acute toxicity: Immediate toxicity
    x) Chronic toxicity: Cumulative toxicity
    y) Atropine: Specific antidote
    z) Activated charcoal: General antidote
    aa) Sedatives/hypnotics: Symptomatic therapy
    bb) Fluids/Electrolytes: Supportive therapy
    cc) Occupational toxicity: Industrial origin
    dd) Environmental toxicity: Food residues
    ee) Measure of acute toxicity: $LD_{50}$

# CHAPTER – 44: TOXICITY OF METALS

## 1. Arsenic

Arsenic is of the most common environmental contaminants. Naturally found in soil, water and air (Groundwater in West Bengal, Bangladesh etc has high As levels)

**Sources:**

A) Release of arsenicals from Cu, Pb and Zn smelters: Contamination of herbage and water.
B) Effluent water from thermal power plants: Contamination of herbage and water.
C) Use of arsenicals as herbicides/weedicides, seed/grain dressings or wood preservatives.
D) Use of arsenical dips for control of ectoparasites in sheep.
E) Use of organic arsenical feed supplements as growth promoters.
F) Inadvertent use of arsenicals as anthelmntics.
G) Use of arsenicals in manufacture of computer chips and semiconductors.

**Forms of Arsenic**

**Inorganic Arsenicals**:

1. Arsenic trioxide (killing cattle for skin)
2. Arsenic pentoxide
3. Sodium or potassium arsenate
4. Sodium or potassium arsenite (main source: sheep dips, insecticide, seed dressing, wood preservative and killing cattle for skin)
5. Lead or Calcium arsenate
6. Copper arsenite (Cheap coloring agent, dye to color paper and artificial flowers, anthelmintic and insecticide)

**Organic Arsenicals**:

A. Aliphatic organic arsenicals (Growth stimulants. Not used now):
1. Acetarsamide and cacodylic acid
2. Monosodium metharsonate (MSMA)
3. Disodium metharsonate (DSMA)

B. Aromatic Organic arsenicals:
1. Thiacetarsamide (against heartworm in dogs)
2. Arsphenamine (Antisyphilitic in humans)
3. Phenylarsonic acid and its salts (Growth stimulants in pig and poultry)

In general the order of toxicity of arsenicals is: Arsine ($AsH_3$) > Trivalent arsenicals (Arsenites, $As^{3+}$) > Pentavalent arsenicals (Arsenates, $As^{5+}$). Inorganic arsenicals are more toxic than organic arsenicals.

**Toxicokinetics**: As initially accumulates in liver. Following continued exposure gets stored in bones, teeth (similarity to phosphorus), skin, hair or keratinized (high –SH content) tissues (hair, hooves and nails: not removable). As does not accumulate in soft tissues (rapid excretion after methylation through urine and feces).

**Mechanisms of Toxicosis**: As has strong affinity to sulfhydral (-SH) groups: Dithiol groups. Trivalent arsenicals (Arsenites) inactivate the lipoic acid by complexing with –SH groups and blocks formation of acetyl, succinyl and propionyl coenzymes (interfering with decarboxylation of ketoacids) and impairment of glycolysis and TCA cycle. As also inactivates glutathione by complexing with its –SH groups. The trivalent As also damages capillaries, especially in GI mucosa (mucosal denudation and necrosis). Pentavalent arsenicals uncouple oxidative phosphorylation by competitive antagonism of IP for ATP synthesis, resulting in formation of an arsenate ester instead of ATP (arsenolysis). As also has local corrosive action on the gastrointestinal mucosa. Arsine (gaseous hydride of $As^{3+}$) causes hemolysis.

**Clinical Signs:**

**Acute**: Involvement of GIT, CVS and kidney. As prefers tissues rich in oxidative enzymes (intestines, liver and kidney). Profuse watery diarrhoea (rice water diarrhoea) blood tinged at times, severe colic, dehydration, weakness, depression, weak pulse and CV failure.

**Subacute**: Colic, anorexia, depression, staggering, weakness, diarrhoea, dehydration, polyurea followed by anuria, paralysis of limbs etc.

**PM Changes**: Intense rose-red inflammation of GIT. Degenerative changes (fatty degenaration to necrosis) in liver and kidney. Preserved carcass.

**Diagnosis**: Sudden onset of illness with gastroenteritis and degenerative changes in liver and kidney and preserved carcass suggest As poisoning. Confirmation by chemical identification of As in stomach contents, liver/kidney or hair/hooves.

**Treatment**: Specific Antidotal Therapy (heavy metal chelators)

1) BAL (Dimercaprol, British anti-lewisite): 2-4 mg/kg (in small animals 10% solution and in large animals 5% solution in 10% benzyl benzoate in GN oil) im three times a day for 2 to 3 days or until recovery.
2) Thioctic acid (Lipoic acid) 50 mg/kg im three times a day as a 20 % solution alone or in combination with BAL 3 mg/kg im every 4 hr for first 2 days four times on third day and twice a day for next 10 days or till recovery
3) D-penicillamine @ 10-50 mg/kg orally, 3-4 times a day for 3-4 days.
4) Sodium thiosulfate: Horses/Cattle: 8-10 G as 10-20% sol iv and 20-30G orally in 300 ml water. Sheep/Goat: 5 -7.5 G orally 100 ml water.
   Small animals: 0.5 – 3 G orally or 20% sol iv @ 30-40 mg/kg 2 or 3 times/day for 3 – 4 days or until recovery.

**2. Mercury**

**Sources**:

a) Contamination of herbage and water by mercurial effluents from the metallurgy.
b) Accidental ingestion of seeds treated with mercurial fungicides and seed dressings.
c) Inadvertent use of mercurial ointments for skin lesions (common in dogs/cats due to licking of wounds).

Minamata disease (1953-60) and Nigata disease (1964-65) in Japan: Minamata and Nigata are small towns in Japan:

✓ Mercurial effluents from industries → Minamata bay/Nigata bay → Plankton algae → Mercurials in fish (biomagnification: about 300 fold or more) → Consumption of fish by people = Disease (locomotor disturbances)/abnormal gait.

**Forms of Mercury**:

**Inorganic Mercurials**:

A. Elemental (liquid) Hg
B. Mercuric chloride (sublimate)
C. Mercurous chloride (calomel : antiseptic, skin creams)
D. Mercurochrome (antiseptic) : Poorly absorbed from GIT, low toxicity.

Acute: Corrosive, vomiting, diarrhoea, colic and renal damage.
Chronic: Neurological disorders

**Organic Mercurials**:

A. **Methyl Hg or Ethyl Hg**: Accumulates in marine fish (biomagnification): Access to brain, kidney and muscle in man and animals.

Inorganic Hg → (Microorganisms) Methyl Hg (River, lakes and sea)

B. **Phenyl Hg**: Fungicide (seed dressing): Nervous disorders.

Mercury is mutagen, teratogen, carcinogen and embryocidal.

**Toxicokinetics:** Elemental Hg is not absorbed from GIT. Hg vapour is lipid soluble, gets absorbed through inhalation, and oxidized to mercuric ions ($Hg^{+2}$), which bind with plasma proteins. The unconverted elemental Hg enters CNS and causes neuronal damage. Inorganic mercurials are only slightly absorbed (2%) from GIT. Organic mercurials are highly absorbed from GIT (up to 90%) and get distributed all over the body, including CNS. Hg is slowly excreted through feces and urine.

**Mechanism of Toxicosis:** Similar to that of arsenic. Mercury even at low concentrations is capable of inactivating –SH containing compounds. Inorganic mercurials cause renal tubular necrosis and hepatotoxicity. Methyl mercury also interacts with –SH groups in DNA and RNA and alters their structural integrity (mutagenicity). Mercuric ion liberated from mercurials causes degenerative changes in nerves and GI tract mucosa.

**Clinical Signs**:
Acute: Nervous signs (excitement, tremors, convulsions and depression). GI disturbances (gastroenteritis, bloody diarrhoea, vomiting with blood and dehydration).
Chronic: Incoordination, altered gait, stumbling, head-pressing, muscle spasms, blood in urine/feces, pale mucosae, epistaxis, Nervous signs are more common in monogastrics than in ruminants.
**Treatment**: Similar to that of Arsenic (specific antidotal therapy).
BAL: 3 mg/kg im every 4 hr on first 2 days, every 6 hr on third day and every 12 hr for next 10 days or until recovery.
D-penicillamine: 15 – 50 mg/kg orally
The other treatment includes:
In acute poisoning as a first aid measure give raw white of egg or milk followed by gastric lavage with saturated sodium bicarbonate sol in dogs/cats. If poisoning is through topical exposure wash the skin thoroughly with soap and water. Fluid/electrolyte therapy is also recommended.

### 3. Lead

**Sources:** Ubiquitous in distribution. All as a result of human activity:

a) Improper disposal of lead articles: Automobile battery casings, used batteries, used up crank case oil, lead paints (lead carbonate: white and lead oxide: red), greases, solder, asphalt, golf balls etc.
b) Industrial effluents (lead smelters): Fumes contain lead oxide, which gets deposited on herbage and also contaminates water resources.
c) Automobile exhausts: Petrol contains tetraethyl lead and tetramethyl lead (antiknock ingredients).
d) Drinking of water supplied through lead pipes.
e) Ingestion of plants treated with insecticide lead arsenate.

**Toxicokinetics**: Has affinity for tissues rich in mitochondria. Erythrocytes, liver and kidney have high Pb levels. From soft tissues it is redistributed to bones. Pb gets deposited in bones ("Sink" for lead since bones contain 95-98% of body load of Pb). When the bones get saturated with Pb, the toxicity signs appear. If exposure is removed, Pb slowly disappears from bones. Lead poisoned cows are a potential public health hazard (excretion in milk).

**Mechanism of Toxicosis:** Multiple actions at subcellular level:

a) Interferes with hematopoiesis, blocks heme biosynthesis (microcytic-hypochromic anaemia) by inhibiting the –SH enzymes: δ aminolevulinate (δ ALA) dehydratase and ferrochelatase: Bones-haemopoiesis).
b) Interferes with the function of Cu, Fe and Zn in enzymatic actions.
c) Inactivates other –SH enzymes: interferes with oxygen utilization, oxidative phosphorylation and ATP formation.
d) Cerebral haemorrhage/oedema: Capillary endothelial damage in CNS.
e) Demyelination in peripheral nerves.
f) Immunosuppression (interferes with antibody production).

**Clinical Signs**: Toxic to haemopoietic system, immunosuppressive, teratogenic and nephrotoxic.
**Acute**: Nervous signs (excitement, bellowing, staggering, muscular spasms/tetany, convulsions)
**Subacute**: Digestive disturbances: Anorexia, constipation or diarrhoea, colic, ruminal atony and vomiting in dogs.
**Chronic:** Plumbism: Locomotor disturbances, rigidity of joints, swaying movements, drop in milk yield, abortion/fetal death. Blue-black or grayish or discoloration or slate color of gums (lead line: along gingival margin in man). Anaemia. Roaring in horses (paralysis of laryngeal muscles). Nervous signs are not common in cattle.
**Diagnosis**: Clinical signs. Estimation of Pb levels in blood (normal: 0.05-0.2 ppm; not physiological), liver and kidney: 10 ppm or more. Blood or urinary δ ALA (> 500 µg/100 ml in Pb poisoning; normal δ ALA levels: 140 µg/100 ml)).
**Treatment:** Specific antidotal therapy: Disodium calcium EDTA chelates bone Pb by forming a readily excretable complex through kidney (Na-EDTA should not to be used).
Livestock: 110 mg/kg divided in 2 treatments sc or iv daily for 3 days. Repeat the course after a of 2 days.
Dogs: Same divided into 4 treatments sc in 5% dextrose for 2-5 days.
Thiamine: 2-5 mg/kg/day sc reduces tissue deposition of Pb (in acute cases up to 30-50 mg/kg/day sc).
D-penicillamine: Dogs: 110 mg/kg/day orally for 2 weeks.
Other Treatment: Saline purgatives (mag sulf: 400 mg/kg orally), corticosteroids (dexamethasone), rumenotomy (and replacement of contents), diazepam/barbiturates or tranquilizers to control convulsions.

## 4. Copper

**Sources:**

1. Ingestion of forage in orchards sprayed with $CuSO_4$ fungicide (Bordeaux mixture: 1-3% $CuSO_4$).
2. Drinking foot rot baths or water from ponds treated with algicidal $CuSO_4$.
3. Contamination of water and forage near Cu mines and processing industries.
4. Feeding of poultry droppings (as NPN source) from chicken treated with $CuSO_4$ (growth promoter).
5. Improperly blended salt licks or mineral mixtures with high copper salts low in molybdenum or inorganic sulfates.
6. Ingestion of *Heliotropium europaenum* or *Senecio* spp. for several months causes hepatogenous chronic Cu poisoning (hepatotoxic alkaloids: retention of Cu in liver).

Sheep are the most susceptible. Acute poisoning in sheep and young calves 20-100 mg/kg and in mature cattle 200-800 mg/kg. Chronic poisoning with daily intakes of 3-5 mg of Cu/kg when grazing pastures that contains 15-20 ppm (DM) of Cu and low levels of molybdenum.

**Mechanisms of Toxicosis:**

(1) Hemolytic Crisis: In blood Cu enters RBC decreases glutathione levels causing peroxidation of lipids in erythrocyte membrane→ RBC become fragile →intravascular haemolysis → haemolytic crisis (not seen in nonruminants: do not store Cu in RBC and liver).
(2) Impairment of Energy Metabolism: Due to inhibition of dihydrolipoyl dehydrogenase and pyruvate/ketoglutarate dehydrogenase system.
(3) Renal Injury: Cu causes glomerular and tubular necrosis. Haemoglobin (due to hemolysis) clogs tubules and aggravates renal damage. – Cer
(4) In sheep chronic Cu poisoning results in anaemia: interferes with iron absorption from GIT.

**Clinical Signs**: Gastroenteritis: diarrhoea: dehydration. Haemolysis, bloody nasal discharge, hemoglobinuria, jaundice and anaemia.

**Treatment**: Daily feeding of ammonium molybdate @ 50 – 500 mg and sodium sulfate @ 250 – 1000 mg per animal for about 3 – 6 weeks. Vitamin C and ammonium tetrathiomolybdate promote Cu excretion.
Prevention: Top dressing pastures with molybdenum @ 70 gm/ha in the form of molybdenized

superphosphate, molybdenum supplementation or restriction of copper intake. [Wilson disease: A genetic disease in which Cu fails to be excreted in bile and accumulates in liver, brain, kidney and RBC (resembling Cu toxicosis). Kayser-Fleischer ring: green or golden pigment ring around the cornea: Cu deposition in descemets membrane].

**5. Molybdenum**

Molybdenum toxicity is also called Molybdenosis, Peat scours, Teart disease, Spectacle disease, Pacing disease, Enzootic ataxia or Sway back disease.

**Sources:**

1. Ingestion of forage and water in Mb rich areas.
2. Contamination of herbage and water from industries and oil refineries.
3. Excessive use of sodium molybdate (plant growth stimulant) in pasture or forage crops.
4. Deficient dietary intake of Copper (Cu deficiency). Cu and Mb are mutually antagonistic. Molybdenosis results in secondary hypocuprosis. Dietary Mb > 10 ppm is toxic (irrespective of dietary Cu levels). Ideal ratio of Cu and Mb in ration = 6 :1, but toxic if less than 2:1
   Ruminants are much more sensitive than nonruminants

**Mechanisms of Toxicosis:**

1. Mb displaces P in bone formation (competitive antagonism): Bone abnormalities.
2. Mb complexes with catechols in rumen (catechols have bacteriostatic effect in rumen): Scouring diarrhoea.
3. Reduced tyrosinase activity interfering with melanin synthesis.

**Clinical Signs:**

1. Watery Diarrhoea: Persistent scouring with passage of liquid feces full of gas bubbles and unpleasant odour (Peat scours or Teart).
2. Dispigmentation of hair coat, noticeable in black animals, especially around the eyes: Spectacled appearance.
3. Hypochromic anaemia (Cu deficiency).
4. Osteoporosis, joint pain: lameness, abnormal gait while walking i.e. pacing (Pacing disease). Stiffness of back and legs. Reluctance to rise. Enzootic ataxia in Australia and Sway Back in UK.
5. Lowered fertility/Reduced conception rate. Delayed puberty in heifers.

**Treatment:**

Scouring: 1 G CuSo4/day in calves and 2G CuSo4/day for adult cattle
Prevention: In high Mb areas top dressing of pastures with 1 % CuSo4 (If excess Mb CuSo4 2-5%).

**6. Selenium** 0.02% Ascorbic acid

Essential trace element @ 0.1 to 0.3 ppm in ration. (Deficiency: WMD in sheep and cattle; Hepatitis dietetica in pigs, exudative diathesis in poultry). But toxic if high levels are ingested. Maximum tolerance 2-5 ppm. Common in forage eating (grazing) animals.

**Sources**: Ingestion of plants in seleniferous soils. Se containing Plants: Three Categories:

A. Obligate Se accumulators: Se indicator or convertor plants: Need Se for growth. Contain Se as high as 10,000 ppm: *Astragalous, Oonopsis, Stanleya, Xylorrhiza* spp.
B. Facultative Se accumulators: Do not require Se for their growth, but take up Se from soil and store it: *Aster, Astriplex, Castillega* spp. Accumulate Se up to 100 ppm.
C. Passive Se accumulators: All plants growing in Se rich areas. Accumulate Se up to 25 ppm.

**Mechanisms of Toxicosis:**

1. Replacement of sulfur in sulfur containing amino acids (cysteine and methionine): formation of abnormal enzymes and proteins in hair and hooves.

2. Inhibition of –SH enzymes (succinic dehydrogenase: reduced ATP synthesis).
3. Interfering with cellular oxidation in muscle tissue through inhibition of heme containing selenoprotein.
4. Stimulation of glutathione peroxidase (Se containing enzyme) activity in liver and RBC (lipid peroxidation).
5. Reduction in tissue vitamin C stores (increased activity of ascorbic acid oxidase).

**Clinical Signs**:
Acute: Rare: Gastrointestinal disturbances, respiration distress, pulmonary oedema and haemorrhages.
Selenosis: It may be subacute or chronic:
Subacute (blind staggers): Ingestion of plants with > 30 ppm of Se for several weeks. Seen in cattle and sheep, but not in pigs or horses. The clinical signs are aimless wandering, walking into objects, impaired vision (corneal opacity), weak fore limbs (going down on knees), paralysis of tongue and throat muscles and subnormal temperature. Death due to respiratory failure.
Chronic (alkali disease, *assumed so due to drinking of alkaline water*): Ingestion of plants containing 5-25 ppm of Se for several weeks to months: Abnormal hooves, cracking of hooves below the coronary band (sloughing of hooves in severe cases), cracks in horns, stiffness of joints, lameness, reluctant to move even for short distances, loss of hair from tail (cigar tail or bob tail) and mane in horses, delayed blood clotting and anaemia. Reduced conception and increase of dead piglets born in sows. In poultry reduced hatchability of eggs and deformed embryos.

**Treatment**: No specific antidote
Arsenic supplementation in feed reduces Se toxicity (As promotes Se excretion): 0.02 % Arsenilic acid in feed or Sodium arsenite in water at 5 ppm level. Protein rich diet (supplementation of S-Containing amino acids). BAL is not used (increases renal damage). Vitamin E should not be given (synergistic with Se).

## 7. Cadmium

Its toxicity is not common in animals; but is of major toxicological concern in man (like lead and mercury); occupational (industrial) toxicity of workers in metal smelters. Cadmium toxicity due to consumption of rice contaminated with cadmium residues (effluents from lead, zinc and cadmium mines) in women with multiple births (six or more pregnancies) characterized by joint and muscle pains was popularly known as *itai-itai* disease.

**Sources**:

a) Ingestion of solder alloys, nickel-cadmium batteries, tyres etc.
b) Contamination of feeds/fodder/pastures with sewage and effluents from smelters.
c) Indiscriminate use of shampoos containing cadmium sulfide.

**Mechanism of Toxicosis**: Inactivates glutathione and sulfur containing aminoacids. It binds to metallothionein (protein rich in cysteine), in kidney the complex is taken up into lysosomes of tubular cells, where cadmium gets released in the cytoplasm which in turn causes degenerative changes in the tubular cells (renal toxicity).

**Clinical Signs**:
Acute: GI disturbances, vomition, abdominal pain, diarrhoea, hepatoxicity and renal toxicity.
Chronic: Pulmonary emphysema/fibrosis, anaema, proteinuria, testicular degeneration, osteoporosis, parakeratosis in pigs and calves (secondary zinc deficiency) and degeneration of ovaries (stoppage of egg laying).

**Treatment**: No specific antidote. Gastric lavage, administration of selenium (forms inactive complex with cadmium), and disodium calcium EDTA as cadmium chelator. BAL (sulfur containing chelator) is contraindicated since the chelate-cadmium is mainly excreted through kidney; where free cadmium is again relessed, aggravating nephrotoxicity.

## EXERCISE

1. Discuss in brief the sources, mechanism of toxicosis, clinical signs, diagnosis and treatment of arsenic toxicity in animals.
2. Discuss in brief the sources, mechanism of toxicosis, clinical signs, diagnosis and treatment of mercury toxicity in animals.
3. Discuss in brief the sources, mechanism of toxicosis, clinical signs, diagnosis and treatment of lead toxicity in animals.
4. Discuss in brief the sources, mechanism of toxicosis, clinical signs, diagnosis and treatment of copper toxicity in animals.
5. Discuss in brief the sources, mechanism of toxicosis, clinical signs, diagnosis and treatment of molybdenum toxicity in animals.
6. Discuss in brief the sources, mechanism of toxicosis, clinical signs, diagnosis and treatment of selenium toxicity in animals.
7. **Write short notes on the following**:
   a) Minamata disease
   b) Plumbism
   c) Alkali disease
   d) Blind staggers
   e) Spectacle disease
   f) Peat scours
   g) Teart disease
   h) Se accumulators
8. **Differentiate between the following pairs**:
   a) Blind staggers and alkali disease
   b) Lewisite and BAL
   c) Antidote and chelate
   d) Minamata disease and pacing disease
   e) Obligate Se accumulators and Facultative Se accumulators
9. **Describe the mechanism of toxicosis/Treatment of the following**:
   a) Arsenic – BAL
   b) Lead – Disod. cal. EDTA
   c) Mercury – BAL
   d) Copper
   e) Molybdenum – Ammonium molybdate, Sodium sulfate, $CuSO_4$
   f) Selenium
10. **What do you mean by the following? Write in one or two sentences for each**:
    a) Minamata disease
    b) Plumbism
    c) Alkali disease
    d) Blind staggers
    e) Spectacle disease
    f) Peat scours
    g) Teart disease
    h) Hemolytic crisis
    i) Chelating agents
    s) Obligate selenium accumulators
    t) Facultative selenium accumulators
    j) BAL
    k) Arsine – gaseous hydride $AsH_3$ (hemolysis)
    l) Sulfhydral groups
    m) Lead line
    n) Nigata disease
    o) Itai-Itai disease – cadmium
    p) Dog murrain
    q) Mercurial ptyalism
    r) Aresnolysis – formation of As-esters instead of ATP
    u) Passive selenium accumulators
11. **Matching** (parallel pairs)
    a) Arsenic: Keratinized tissues
    b) Lead: Bone
    c) Lewisite: Warfare agent
    d) BAL: Dimercaprol
    e) Arsenic: Rice water diarrhea
    f) Arsenic: Preserved carcass
    g) Methyl Hg: Minamata disease
    h) Lead: Plumbism
    i) Lead: Microcytic-hypochromic anaemia
    j) Copper: Haemolytic crisis
    k) Lead; Roaring in horses
    l) Lead: Disoidium calcium EDTA
    m) Arsenic: BAL
    z) *Astragalus* spp.: Selenium accumulator
    a) Oonopsis spp.: Obligate Se accumulator
    b) *Heliotropium* spp. Copper retention in liver
    f) *Aster* spp. Facultative Se accumulator
    g) Cigar tail/Bob tail: Selenosis
    h) Blue line: Lead
    i) Barium: Bone seeker
    n) Copper: Foot rot baths
    o) Copper: Bordeaux mixture
    p) Molybdenosis: Spectacle disease
    q) Molybdenosis: Peat scours
    r) Molybdenosis: Teart disease
    s) Molybdenosis: Pacing disease
    t) Molybdenosis: Osteoporosis
    u) Molybdenosis: Hypocuprosis
    v) Hypercuprosis: Molydenum deficiency
    w) Alkali disease: Chronic selenium toxicity
    x) Blind staggers: Subacute selenium toxicity
    y) *Senecio* spp.: Copper retention in liver

j) Itai-Itai disease: Cadmium toxicity
k) Lead: Delta ALA
l) Arsenic: Lipoic acid
m) Selenium: Glutathione peroxidase
n) Copper: Ammonium molybdate
o) Molybdenosis: Copper sulfate
p) Selenosis: Sulfates
q) Necrosis of GI mucosa: Arsenic
r) Radio opacity of long bones: Lead
s) Hoof abnormalities: Selenosis
t) Dispigmentation of hair: Molybdenum
u) Paints: Lead toxicity
v) Foot rot bath: Copper toxicity
w) Ferrochelatase inhibition: Lead
x) *Heliotropium* spp.: Hepatogenous Cu poisning
y) Spectacle disease: Molybdenosis

12. **Substantiate each of the following statements by giving the most appropriate reason:**
a) Hairs/nails are of forensic importance in arsenic poisoning.
b) Pentavalent arsenical uncouple oxidative phosphorylation.
c) Arsenic impairs decarboxylation of ketoacids, glycolysis and TCA cycle.
d) Dimercaprol is the specific antidote for arsenic toxicity.
e) Minamata disease is characterized by locomotor disturbances.
f) Inorganic mercurials are converted to methyl mercury in sea, rivers and lakes.
g) Plumbism is characterized by microcytic-hypochromic anaemia.
h) Heme biosynthesis is blocked by lead.
i) Bones are called as 'sink for lead'.
j) Plumbism in horses results in roaring.
k) Molybdenosis results in osteoporosis.
l) Disodium calcium EDTA, but not the disodium EDTA is the antidote of lead poisoning.
m) *Heliotropium* or *Senecio* spp. Cause hepatogenous chronic copper poisoning.
n) Copper poisoning in sheep is characterized by hemolytic crisis.
o) Hemolytic crisis is not seen in chronic copper toxicity in nonruminants.
p) Chronic copper poisoning causes renal damage.
q) Haemoglobinuria is seen in chronic copper poisoning in sheep.
r) Molybdenosis is also called spectacle disease.
s) Molybdenosis is also called peat scours.
t) Molybdenosis is also called teart disease.
u) Molybdenosis is also called pacing disease.
v) Molybdenosis is also called sway back disease.
w) Molybdenosis results in secondary hypocuprosis.
x) Hypercuprosis results in secondary hypomolybdenosis.
y) Alkali disease is characterized by hoof abnormalties/lameness.
z) Alkali disease in horses leads to cigar tail/bobtail.
a) Subacute selenium toxicity is called blind staggers.
b) Protein-rich diet should be given to animals recovering from selenosis.
c) Arsenic feed supplementation is recommended in selenosis.
d) Lipoic acid is a specific antidote in arsenic poisoning.
e) Selenosis in dogs is also called dog murrain.
f) Nigeta/Minimata disease is related with mercury poisoning.
g) Molybdenosis in calves results in scouring.
h) Selenium compounds are used in treating cadmium toxicity.
i) BAL is not used as an antidote in cadmium toxicity.
j) Disodium calcium EDTA is used in treating cadmium toxicity.
k) Cadmium toxicity leads to parakeratosis in pigs and calves.
l) Cadmium toxicity in hens prevents egg laying.

# CHAPTER – 45: TOXICITY OF NON METALS

## 1. Fluorine

**Sources:** Naturally present in varying concentrations in soil, water and plants.

1. Industrial pollutions: Al, steel, fertilizers, brick kilns, potteries and glass factories.
2. Ingestion of forage and water in Fl rich areas (soils).
3. Ingestion of faulty supplemented feeds (high levels of rock phosphate)
4. Acute: High dose of NaF as anthelmintic.
5. Accidental ingestion of Fl based rodenticides: Na Fluro acetate.

In humans 1 ppm in water prevents dental caries. In animals 1-2 ppm in ration is adequate. Max. Tolerable levels: Cattle and Horses: 40-50 ppm; Chicken: 200 ppm.

**Mechanisms of Toxicosis**: About 95 % of ingested fluoride is stored in bones and teeth. Causes Osteo fluorosis and dental fluorosis. Fluoride inhibits enzymes (proteolytic enzymes and phosphatases) that participate in formation of bones and teeth. Fluoride has high affinity for Ca and replaces the hydroxyl groups in mineral part of bone, which is normally hydroxyapatite. In presence of Fl hydroxyapatite is replaced by fluoroapatite. Fl damages amyloblasts. Formation of abnormal osteoid, poor bony matrix and faulty mineralization of bones. Damage to odontoblasts (blast cells) mineralization of pre-enamel, predentine and precementum are delayed.

**Clinical Signs**:

Acute: Gastroenteritis and nervous signs followed within a few hours by collapse and death.

Chronic (Fluorosis): Bone changes (**Skeletal Fluorosis/Osteofluorosis**): Exostoses. Metabolically active bones are first affected (ribs, mandible and long bones). Growing bones in the young are most affected. Animals are lame. **Dental Fluorosis**: Chalkiness or mottling, staining (yellow, green, brown or black spots), brittle and easily breakable teeth and irregular ware or shedding of teeth, painful mastication: off feed.

**Diagnosis**: Analysis of Fl in water, feed, urine. Clinical signs: Bone (lameness) and teeth defects

**Treatment:**

1. Remove the source
2. Feeding @ 30 gm/animal: calcium carbonate, aluminum oxide, aluminum sulfate, magnesium metasilicate or boron decrease Fl absorption and increase Fl excretion; exerts some control of fluorosis, but no treatment cures the defects.
3. Dietary supplementation of Ca, P and vitamin D
4. Supportive: Corticosterroids, analgesics, antibiotics and fluid therapy.

## 2. Nitrates/Nitrites

**Sources:**

1. Ingestion of nitrate/nitrite through forage and plants: Nitrate rich plants: Accumulate Nitrate: *Amaranthus, Astragalus, Brassica, Ipomoea, Sorghum, Chenopodium* Spp, *Beta vulgaris, Zea mays* etc. Improperly stored hay (damp) or silage: microbial reduction of nitrate to nitrite. Phenoxy acetic acid derivative herbicides: 2, 4-D and 2,4,5-T increase nitrate content of grasses.
2. Agricultural Source: Fertilizers: Runoff water from agricultural fields sprayed with nitrate fertilizers contaminating water in ponds. Accidental ingestion of nitrate fertilizers.
3. Chronic drinking of well water in nitrate rich areas.
4. Excess use of Na nitrite in HCN poisoning.
5. Drinking refuge water from meat processing plants: Nitrates/nitrites used in pickling and curing brines for preserving meats.

Ruminants > sensitive than nonruminants: Ruminal microfloral reduction of nitrate to nitrite (intermediate of ammonia formation). Cattle are the most susceptible. Among nonruminants: Young pigs: reduction of nitrate to nitrite by intestinal microflora, but not in adults (age limited pathway). Simultaneous feeding on subabul increases nitrate toxicity: favours conversion of nitrate to nitrite. Pre-existing anaemia aggravates nitrate toxicity. Cereal based/concentrate diets reduce nitrate toxicity (carbohydrate rich diets).

**Toxicokinetics:** Normally nitrates ingested in limited quantities are utilized for synthesis of proteins through reduction to nitrite and formation of ammonia with the help of ruminal microflora.

Ruminal microfolora — Ruminal microflora

Nitrate → Nitrite → $N_2O$ → $NH_2OH$ → Ammonia → Protein synthesis

Rate limiting reaction

If excess nitrates are ingested or the reduction of nitrate exceeds the ruminal microbial reduction of nitrite to ammonia, nitrites accumulate in rumen and absorbed resulting in toxicity.

**Mechanisms of Toxicosis**: Methaemoglobinaemia and Vascular Shock:

Nitrite combines with Haemoglobin; methaemoglobin: tissue hypoxia/anoxia. Tissue death due to oxystarvation.

Hypotension: Nitrite ions ($NO^-$) formed from nitrate relax vascular smooth muscles: Dilatation of blood vessels: pooling of blood in large blood vessels: decreased venous return: reduced cardiac out put (Vascular shock)

**Clinical Signs**:

Acute: Signs appear if 20-40% haemoglobin is converted to methaemoglobin and death if 80% or more of haemoglobin is converted to methaemoglobin. The signs are respiratory distress (hypoxia/anoxia), gasping, rapid respiration and heart rates, rapid and weak pulse, terminal convulsions, coma and death.

Other signs: Salivation, diarrhoea, colic, muscular weakness, ataxia. In pregnant animals abortion (due to decrease in progesterone concentration) and also the nitrites cross placenta and cause foetal death.

Chronic: Hypothyroidism, Vitamin A deficiency, infertility, immunosuppression.

**Necropsy**: Chocolate or coffee colored blood. Generalized cyanosis.

**Diagnosis**: Analysis of rumen contents for nitrate/nitrite: Blood (> 20 µg/ml). If PM delayed specimens for toxic analysis: aqueous humor or CSF.

**Treatment**: Specific Antidotal Therapy: Regeneration of haemoglobin from methaemoglobin:

Reduction

Methylene Blue → Leuco Methylene Blue (reducing agent)

↓

↓ Activation of Diaphorase I and II

Nitrite

Haemoglobin ($Fe^{++}$) → Methaemoglonin ($Fe^{+++}$) → Haemoglobin ($Fe^{++}$)

Oxidation — Reduction

Leuco methylene blue activates Diaphorase I and II, which facilitate reduction of methaemoglobin to haemoglobin.

Methylene blue as 1% sol by slow iv injection @ 8.8 mg/kg in ruminants or 4.4 mg/kg in nonruminants. Repeat after 15-30 min if clinical response is not satisfactory.

Ascorbic acid as reducing agent 5 – 20 mg/kg iv.

**Supportive treatment**: Blood transfusion, shock therapy (adrenaline to increase BP). Broad spectrum antibiotics through large volumes of water into rumen to reduce ruminal microfloral reduction of nitrates to nitrites. Mineral oil (liquid paraffin) or saline purgatives to expel nitrates/nitrites from GIT.

**3. Oxalates** — 22gm/animal/day dicalcium phosphate.

**Source:** Primarily results from ingestion of plants rich in oxalates. Plants containing **> 10% oxalates** (on DMB) are toxic. Oxalate rich plants are very palatable to livestock. The oxalate rich plants are: *Amaranthus retroflexus*, *Atriplex* spp., *Beta vulgaris*, *Calandrina* spp., *Oxalis* spp., *Rumex* spp., *Setaria* spp. and *Trianthema* spp. Large amounts of oxalic acid are formed on damp hay/straw or silage infested with *Aspergillus niger* or *A. flavis*. Fresh sugar beet tops contain large quantities of oxalates and nitrates. The poisoning is commonly seen in sheep suddenly shifted to oxalate pastures, whereas, the sheep accustomed to oxalates can consume larger quantities of the grasses without ill effects.

**Toxicokinetics:** Sodium or potassium oxalates and oxalic acid are soluble and calcium oxalate is insoluble in the rumen. Soluble oxalates are detoxicated through conversion to carbonates and bicarbonates or formation of insoluble calcium oxalates, which are excreted through feces. However, if excess oxalates are

ingested i.e. beyond the ruminal capacity of its detoxification, oxalates are absorbed unchanged and produce toxicity.

**Mechanism of Toxicosis:**

a) Calcium metabolism is upset (oxalates chelate $Ca^{++}$ causing acute hypocalcaemia), interfering with milk production in lactating animals and foetal bone growth in pregnant animals.
b) Blocking of renal tubules by calcium oxalate crystals - renal injury.
c) Failure of blood clotting mechanisms and haemolysis.
d) Oxalates also crystallize and cause neuronal damage in brain – CNS signs and paralysis.

**Clinical Signs:** Dullness, anorexia, lowered head, keeps isolated from the herd, salivation, nasal discharge, weakness, rapid shallow breathing and collapse.
**Necropsy:** Accumulation of calcium oxalate crystals in kidneys and urinary tract. Lungs filled with dark red blood. Petechial haemorrhages in visceral organs and heart.
**Treatment:** Shift to oxalate-free pastures. Oral administration of **dicalcium phosphate** (25% in salt ration) or given as grain or alfalfa hay pellets containing 10% dicalcium phosphate @ 225 G/animal/day for **elimination of oxalates (calcium oxalate) through feces.** Prior treatment with dicalcium phosphate before allowing sheep to graze in oxalate rich pastures, does not result in oxalate poisoning.

**4. Salt**

Occurs in all species. Pigs most sensitive followed by Poultry and cattle. Sheep are relatively resistant. Dogs are least susceptible. Recommended salt intake in drinking water (all species) = less than 0.5 %
Acute oral LD in pigs = 2.2 gm/kg; Sheep = 6 gm/kg
**Sources:** Salt poisoning is directly related to water deprivation or water withholding.

1. Feeds with high salt levels with restricted/limited/reduced water intake. Toxicity in pigs at 0.25% in feed with limited water intake, but no toxicity up to 13% salt in feed with adequate fresh water intake.
2. Excessive licking of salt licks especially by salt hungry animals (deprived of salt for quite some time: develop craving for salt).
3. Feeding on salty meat, ingestion of brine from butchers shop, salty whey from cheese factories or salted fish waste.

**Mechanism of Toxicosis:** Disturbed Na and Water balance

a. Excessive salt in feed: Excess Na ion in GIT: Water secretion in GI lumen (Osmotic): diarrhoea: dehydration: constipation.
b. After absorption: Hypertonicity of blood → extracellular hypertonicity: Shrinkage of capillary endothelial cells (brain and meninges): increased capillary permeability: accumulation of fluid in interstitial spaces: Cerebral oedema.
c. Hypernatreamia: Stimulation of Osmoreceptors: Excessive thirst.
d. Over hydration of central neurons due to elevated Na ion:
e. Excess Na in renal tubules, shrinkage of renal tubular cells: polyurea. Deposition of NaCl crystals in tubules: Tubular damage: anuria: Uremia.

**Clinical Signs:**
GIT: Excessive thirst, salivation, diarrhoea, dehydration followed by constipation and gastroenteritis.
Renal: Polyurea followed by oliguria/hematuria and anuria.
Nervous: Hyperirritability, rigidity of muscles, stumbling, ataxia, blindness, knuckling of fetlocks, terminal clonic/tonic convulsions, paralysis, coma and death.
In poultry: Fluid discharge from beak, watery fecal droppings and leg paralysis, drop in egg production and egg shell deformities.
Eosinopaenia in Pigs: Eosinophil aggregation or accumulation in brain: Eosiniphilc cuffs around blood vessels in cerebral cortex and adjacent meninges.

**Diagnosis**: History, clinical signs and extracellular Na ion levels: Serum or Plasma and CSF more than 160 meq/litre; Brain more than 1800 ppm

**Treatment**:

Removal of offending feed/water and give salt free fresh potable water (to start with small volumes and gradually increase: Excess water initially aggravates cerebral oedema).

Symptomatic treatment: Rehydration (fluid therapy) and sedatives.

**5. Urea** – 5% acetic acid 2-8 Lit in Cattle

Urea intoxication is NPN toxicosis. Acute urea ingestion is highly fatal. Mature ruminants are most sensitive (Presence of urease in functional rumen i.e. after 50 days of age). Horses and pigs are relatively resistant, but among monogastrics horses are more susceptible.

**Sources**:

1. Excessive addition of urea to animal feeds/fodder as cheap source of NPN.
   Feeding of urea-molasses blocks or hay/silage fortified with urea or urea-molasses (increased palatability). Poisoning occurs in unaccustommed animals when dietary urea level = 0.3 – 0.5 gm/kg body weight and at 1 – 1.5 gm/kg body weight is lethal. Increase urea supplementation gradually up to desired level. Tolerance developed lasts for 3 or 4 days after discontinuation. Livestock need days or weeks for total adaptation before rumen microflora can utilize the gradually increasing amounts of urea. Simultaneous feeding of soybean meal potentiates urea toxicity (excessive ammonia formation in rumen due to urease in soybean). Ammonium salts @ 0.3 – 0.5 gm/kg toxic in all species and ages.
2. Accidental ingestion of urea phosphate fertilizer.

**Mechanism of Toxicosis**:

Toxicity of urea/NPN is due to formation of excess ammonia by rumen microflora and its absorption. Hyperammonemia: inhibition of TCA cycle (particularly in CNS). Enhanced glycolysis: increased lactic acid formation: Metabolic acidosis.

**Clinical Signs**: Muscle tremors (face and ears) and incoordination, exophthalmia, abdominal pain, frothy salivation, ruminal atony, tympany, polyuria, dehydration, pulmonary oedema, dyspnoea, gasping, bellowing, tetanic spasms, struggling and terminal strychnine-like convulsions

Cattle: Wildly aberrant behaviour: Syndrome called: "Bovine Bonkers"

**Diagnosis:** History, clinical signs, analysis of rumen liquor for ammonia (> 800 ppm) and blood (≥ 20 ppm).

**Treatment**:

1. Ruminal infusion or oral admnistration of 5% acetic acid (2-8 L in cattle; 0.5-2 L in Sheep and goats) and concomitant infusion of iced (0-4°C) water (up to 40 liters in cattle and less in sheep and goats). Acetic acid lowers rumen pH and prevents ammonia absorption and inactivates preformed ammonia (ammonium acetate) which is utilized by rumen microbes. Cold water lowers ruminal temperature and slows down urease activity.
2. Replacing ruminal contents with hay slurry or contents from healthy animals.
3. Correction of tympany: trocar may be installed to prevent recurrence.
4. Supportive: IV saline (dehydration) and calcium gluconate and magnesium sulfate or pentobarbitone sodium IV to relieve teatanic spasms/convulsions.

EXERCISE

1. Describe the sources, mechanism of toxicosis, clinical signs and treatment of fluorosis in animals.
2. Describe the sources, mechanism of toxicosis, clinical signs and treatment of nitrate toxicity in animals.
3. Describe the sources, mechanism of toxicosis, clinical signs and treatment of oxalate poisoning in animals.
4. Describe the sources, mechanism of toxicosis, clinical signs and treatment of salt poisoning in animals.
5. Describe the sources, mechanism of toxicosis, clinical signs and treatment of urea/NPN toxicity in animals.
6. **Write a short note on the following**:
   a) Skeletal fluorosis
   b) Dental fluorosis
   c) Nitrite toxicity
   d) Oxalate toxicity
   e) Ammonia toxicosis

7. **State the mechanism of toxicosis of the following:**
   a) Fluorine
   b) Nitrate
   c) Oxalates
   d) Salt
   e) Urea/NPN

8. **Give the line of treatment of the following toxicities in animals:**
   a) Fluorosis
   b) Nitrate
   c) Oxalosis ~ Di-Calc phosphate
   d) Salt
   e) Urea/NPN

9. **Matching** (parallel pairs):
   a) Methaemoglobin: Nitrate/Nitrite
   b) Renal injury: Oxalates
   c) Haemorrhages: Oxalates
   d) Mottling of teeth: Fluorosis
   e) Exostoses of bone: Fluorosis
   f) Fluorosis: Calcium carbonate
   g) *Ipomoea* spp.: Nitrate rich
   h) Nitrate poisoning: Methylene blue
   i) *Amaranthus* spp.: Oxalate rich
   j) Hypoxia: Nitrites
   k) Oxalosis: Dicalcium phosphate
   l) Salt poisoning: Cerebral oedema
   m) Salt poisoning: Water deprivation
   n) Oxalates: Delayed blood clotting
   o) Oxalates: Hypocalcaemia
   p) Salt poisoning: Excessive thirst
   q) Urea poisoning: Metabolic acidosis
   r) Urea toxicity: Bovine bonkers
   s) Urea toxicity: Dilute acetic acid
   t) Chocolate colored blood: Nitrate toxicity
   u) Shifting lameness: Fluorosis
   v) Ammonical odour: Urea toxicity
   w) Crystals in brain: Oxalate toxicity
   x) Urea toxicity: Vinegar
   y) Soybean meal: Urea toxicity
   z) Spoiled hay: Nitrate/Oxalate toxicity

10. **What do you mean by the following? Answer in one or two sentences for each.**
    a) Osteofluorosis
    b) Dental fluorosis
    c) Methaemoglobinaemia
    d) Ammonia toxicosis
    e) Bovine bonkers

11. **Substantiate each of the following statements by giving the most appropriate reason in one or two sentences.**
    a) Fluorosis is characterized by dental and skeletal abnormalities.
    b) Cattle with fluorosis remain off feed.
    c) Bullocks with fluorosis exhibit lameness.
    d) Ruminants are more susceptible to nitrate toxicity than the monogastrics.
    e) *Lucaena* (subabul) feeding aggravates nitrate toxicity.
    f) Piglets are more sensitive to nitrate toxicity than the adult pigs.
    g) Nitrate toxicity results in hypoxia/respiratory distress.
    h) Nitrate toxicity may also lead to vascular shock.
    i) Methylene blue is the antidote in nitrate poisoning.
    j) Nitrate toxicity is due to failure of cellular respiration.
    k) Ingestion of damp hay may cause nitrate poisoning.
    l) 2,4-D or 2,4,5-T pretreatment aggravates nitrate toxicity.
    m) Ingestion of mold-infested hay/silage predisposes to oxalate toxicity.
    n) Feeding of fresh sugar beet tops may cause toxicity in cattle.
    o) Calcium metabolism is upset in oxalate toxicity.
    p) Oxalate poisoning reduces milk yield of cows.
    q) Oxalate toxicity is characterized by renal impairment
    r) Oxalate poisoning results in delayed blood clotting.
    s) Neurological signs appear in oxalate toxicity.
    t) Dicalcium phosphate prevents oxalate toxicity.
    u) Excess salt ingestion causes diarrhea.
    v) Salt toxicosis leads to cerebral edema.
    w) Metabolic acidosis is observed in urea toxicosis.
    x) Ruminal infusion of dilute acetic acid is used to prevent urea toxicity.
    y) Ruminal infusion of cold water prevents urea intoxication.
    z) Soybean meal potentiates urea intoxication.

# CHAPTER – 46: TOXICITY OF AGROCHEMICALS

Agrochemicals are of two major groups:

1) Fertilizers: Nitrate, Phosphorus and Urea
2) Pesticides: Substances or mixtures of substances intended for preventing, destroying, repelling or mitigating any pest.

A pest is an uneconomical, undesirable or harmful species that adversely affect the economic, desirable or beneficial species. Pesticides are used to kill the pests. Therefore, the pesticides include: Insecticides (In crops, man or animals), parasiticides (Ecto and Endo), fungicides (Crops and Seeds), weedicides or herbicides and rodenticides.

## 1. Insecticides

**Classification of Insecticides:**

**Natural Insecticides:** Nicotine (from leaves of *Nicotiana tabacum)*, Pyrethrum (from flower heads of *Chrysanthemum cinarariaefolium*) Derris powder (from rhizome of *Derris eclipta*).

**Organochlorine Insecticides** (OCI): Three categories: A. Chlorinated ethane derivatives (DDT, DDE DDD or diicofol). B. Cyclodienes (Aldrin, dieldrin, endrin, chlordane, heptachlor). C. Hexachlorocyclohexanes (BHC, lindane).

**Organic Phosphate Insecticides** (OPI): Parathion, malathion, diazinon, dimethoate, fenitrothion, anilophos, leptophos etc.

**Carbamate Insecticides**: Aldicarb, carbaryl, benfuracarb, butocarboxim, carbofuran, methomyl etc.

**Pyrethroid Insecticides**: Alletrhrin, permethrin, cypermethrin, deltamethrin, flumethrine, fenvalerate etc.

**Sources of Insecticide Toxicity**: Accidental, indiscriminate and malicious

Accidental: Ingestion of recently pesticide sprayed crops

A. Drinking of water from pesticide sprayed paddy fields
B. Licking or Ingestion of pesticide emptied containers (bags/cartoons)
C. Contamination of forage or water due to drift of pesticides during aerial spray.
D. Ingestion of pesticide treated seeds
E. Improper storage of pesticides and animal feeds at same place
F. Indiscriminate use:
    a. Dermal sprays of insecticide on wounds and/or in oily solvents for control ectoparasites
    b. Improper use of insecticides in public health programmes
    c. Poisoning in young stock due to suckling of milk from poisoned dams.
    d. Improper sprays of animal quarters
G. Malicious Killing.

**Mechanism of Toxicosis:**

1. i) Organic Phosphate Insecticides: Irreversible AChE inhibition: ACh accumulation in nerves and neuroeffector junctions: parasympathetic or cholinergic signs. Majority are not potent antiChEs *in vitro* until they are activated to potent AntiChEs (oxygen analogs) *in vivo* by hepatic microsomal oxidases (lethal synthesis or metabolic activation); such compounds are called indirectly acting: Parathion to paraoxon; malathion to malaoxon; fenthion to fenoxon; and sumithion to sumioxon. The compounds which need no such metabolic activation are called direct acting, their activity *in vitro* = *in vivo*: Dichlorvos, diazinon, dimethoate, DFP, TEPP etc.
   ii) Carbamate Insecticides: Reversible AChE inhibitors: Direct acting .Their antiChE activity *in vitro* = *in vivo*.

2. Organochlorine insecticides: Nerve poisons or neurotoxic insecticdes (high lipid solubility), act by interfering with NAP in sensory and mtor nerves. Selectively toxic to insects (rapid absorption through chitinous cuticle of insects; but not (relatively) through intact skin of animals). DDT, DDE or DDD increase the duration of opening of $Na^+$ channel causing delayed repolarization resulting in repetitive discharge from small stimuli. The cyclodienes and hexachlorocyclohexanes interfere with the function of inhibitory transmitter GABA causing depolarization of postsynaptic membrane and repetitive discharge. The increased excitability is followed by paralysis of motor nerves.
3. Pyrethroids: Nerve poisons like DDT. Prolonged depolarization (delayed closure of Na channels and repetitive discharge. Piperonyl butoxide and piperonyl cyclonene potentiate pyrethoid insecticidal and mammalian toxicity (inhibition of mixed function microsomal oxidases i.e. by preventing detoxification of pyrethroids. Pyrethroids are relatively less toxic in mammals and birds, but highly toxic to fish.

**Clinical Signs**:

1. Organic Phosphate and Carbamate Insecticides:
   Muscarinic signs: Profuse salivation (watery drooling), bronchial secretions and constriction, diarrhea, frequent urination and miosis.
   Nicotinic signs: Muscular tremors, convulsions, paralysis of respiratory muscles and dyspnoea.
   CNS signs: Restlessness, ataxia, depression of respiratory and vasomotor centres, paralysis, coma and death due to respiration failure followed by cardiovascular failure.
   Some OPI like tri-ortho cresyl phosphate (TOCP), diisopropyl phosphorofluoridate (DFP), EPN (Ethyl nitrophenyl phosphonothioate), leptophos, mipafox etc produce **delayed neurotoxicity** after 8 to 21 days of exposure. These compounds are weak ChE inhibitors but strongly inhibit neurotoxic esterase (NtE) in brain and spinal cord causing axonal swelling, breakdown and demyelination of spinal and peripheral neurons. The signs of delayed neurotoxicity include muscle weakness, ataxia, flaccid paralysis of limbs. Poultry birds are the most sensitive spp.

2. Organochlorine and Pyrethroid Insecticides: Mainly behavioural and nervous signs: Anxiety, aggressiveness, jumping over unseen objects, wall climbing, hypersensitive to external stimuli, fasciculations/twitching of facial and eyelid muscles. Spasms of fore and hind quarter muscles, champing of jaw, hyperthermia, dyspnoea, terminal convulsions, collapse and death (due to respiratory failure). In addition some autonomic signs like mild salivation (frothy), mydriasis and urination are also seen.

**Diagnosis**: History, circumstantial evidence, clinical signs, estimation of blood ChE activity (25% or more decrease in OPI and carbamate toxicity) and identification of the insecticide in feed, water, ruminal content or tissues.

**Treatment**:

OPI: Specific antidotes: a) Muscarinic blockers b) ChE reactivators 2) Reduce absorption

a) Atropine $SO_4$: Dogs and Cats: 0.2-2 mg/kg (cats lower side) 1/3 iv and rest sc. Repeat every 3-6 hr as required. Horse and Pig: 0.1-0.2 mg/kg I/V, repeat every 10-15 min as needed; Cattle and sheep: 0.5-1 mg/kg 1/3 iv and rest im or sc, repeat as needed. Over dosage of atropine to be avoided.
b) 2-PAM (2-Pyridine aldoxime methiodide, 2-PAM chloride) @ 20-50 mg/kg as 10% sol im or slow iv (if rapid respiration arrest) repeat if necessary. ChE activation decreases with time (after exposure), better to use within 24-48 hr.
c) If ingestion: Emetics, purgatives, activated charcoal (3-6 g/kg as slurry in water. If dermal wash with soap and cool water.

Carbamates: Atropine sulfate only as above, but not ChE-reactivators.

OCI and Pyrethroids: No specific antidote:

Symptomatic Treatment: Excitement and nervous signs (barbiturates, chloral hydrate or diazepam), respiratory depression (analeptics).

Reduce Absorption: Saline purgatives (not oily), gastric lavage
Supportive Treatment: IV fluid and electrolyte therapy.

## 2. Herbicides

**Classification of Herbicides:**

| Group | Examples |
|---|---|
| Chlorophenoxy/Phenoxyacetic acid Compounds | 2,4-D : Dichlorophenoxyacetic acid<br>2,4,5-T : Trichlorophenoxyacetic acid |
| Bipyridinium/Bipyridyl Compounds | Diquat, Paraquat |
| Triazine Derivatives | Atrazine, propazine,simazine,metribuzin |
| Chlorobenzoic acid derivatives | 2,3,6-TBA : trichlorobenzoic acid |
| Dinitrophenol Derivatives | Dinitrophenol (DNP), dinitroorthocresol (DNOC) and dinoseb (DNBP) |
| Phenylurea Derivatives | Diuron, fenuron, monuron, isoproturon |
| | Glyphosate and Sodium Chlorate |

**Sources:**

a. Accidental ingestion of herbicide spills.
b. Grazing in recently herbicide-sprayed fields.
b. Improper disposal of herbicide spills.
c. Malicious poisoning.

**Chlorophenoxy Compounds** (Phenoxyacetic acid compounds):
Mechanism of Toxicosis: Not known. Cause cytotoxicity to visceral and reproductive organs. Interfere with neuromuscular transmission. Increase HCN and nitrate content and palatability of such plants.
Signs and Symptoms: Anorexia, diarrhoea, muscle weakness, incoordination and metabolic acidosis.

**Triazine Compounds:**
Mechanism of Toxicosis: Not known.
Signs and Symptoms: Like Chlorophenoxy compounds.

**Phenylurea Derivatives:**
Mechanism of Toxicosis: Not known.
Signs and Symptoms: Like Chlorophenoxy compounds. Induce hepatic microsomal oxidases (alter effects of xenobiotics)

**Bipyridal/Bipyridinium Compounds:**
Mechanism of Toxicosis: Paraquat causes pulmonary toxicity due to damage of the pneumocytes and alveolar fibrosis; release of PGs and proliferation of fibroblasts in lungs – interfere with exchange of gases. The paraquat cytotoxicity is due to formation of superoxide and oxygen free radicals ($O_2^-$). Inhibit synthesis of DNA and phospholipids. Lungs are deficient in super oxide dismutase enzyme activity, which converts superoxide to $H_2O_2$ and $O_2$. Hence pulmonary lesions are caused by paraquat. Diaquat causes GI and CNS toxicity, but not the pulmonary toxicity; the mode of toxicosis is not understood.
Signs and Symptoms: Anorexia, abdominal pain, vomiting, pulmonary oedema, dyspnoea, jaundice, tachycardia, corneal opacity, ulceration of mm and skin, cyanosis.

**Dinitropheol Derivatives**: The dinitro phenol derivatives possess insecticidal, fungicidal, acaricidal and herbicidal actions; highly toxic to mammals.
Mechanism of Toxicosis: These uncouple oxidative phosphorylation. In ruminants – the dinitro derivatives are converted to nitrates, which in turn to nitrites, which after absorption cause methaemoglobinemia. Deplete liver glycogen.

Signs and Symptoms: Hyperthermia, dyspnoea, acidosis, tachycardia, convulsions, coma and death. Yellow skin, conjunctiva or hair. Corneal opacity (cataract).

**Sodium Chlorate**: Rarely used. Causes hemolysis and methaemoglobin formation.
**Chlorobenzoic acid derivatives**: 2,3,6 – Trichlorobenzoic acid (2,3,6-TBA)
Mechanism of Toxicosis: Not known.
Signs and Symptoms: Like Chlorophenoxy compounds.
**Treatment of Herbicide Poisoning**: No specific antidotes; symptomatic and supportive treatment.

### 3. Fungicides

These are agrochemicals used to prevent or control fungal infestation of grains, seeds, fruits, vegetables, orchard plants or field crops. Fungicides are classified as inorganic and organic fungicides.

**Inorganic Fungicides**:

a) Sulfur: Its toxicity is due to its oxidation compounds (sulfur dioxide, sulfur trioxide and thiosulfuric acid) or formation of hydrogen sulfide. Its toxicity is also due to its cross linking of proteins or through formation of free radicals. Sulfur is toxic to cattle, horse and poultry. The signs of toxicity include colic, gastroenteritis and diarrhoea. Treatment of toxicity is symptomatic.

b) Bordeaux mixture (copper sulfate + calcium hydroxide): See copper toxicity (metal toxicity).

c) Cadmium chloride: See cadmium toxicity (metal toxicity).

**Organic Fungicides**:

a) Organomercury compounds: Phenylmercury chloride and phenylmercury acetate: See mercury toxicity (metal toxicity).

b) Chlorophenols: Pentachlorophenol (PCP): It is a fungicide, molluscicide, insecticide, herbicide and wood preservative. Their toxicity is due to uncoupling of oxidative phosphorylation.

c) Dithiocarbamates: Ziram, febam, zineb, maneb, thiram etc: Cause GI disturbances and nervous toxicity.

d) Phthalimides: Captan, flopet and captofol: More toxic to ruminants than other animals; cause dyspnoea, ascites, hydrothorax and gastroenteritis.

### 4. Fumigants

These are used as grain protectants against insects in the form of fumigation (gaseous) and also to kill the rodents (as baits like rodenticides). The fumigants are either easily volatile liquids or solids capable of liberating gases. Fumigants are used in closed rooms or chambers or containers. These as insecticides, being in gaseous form, are also effective against insects in the burrows (like bed bugs) not usually accessible to conventional pesticides.

**Inorganic Fumigants**:

a) Aluminium phosphide exerts action through liberation of phosphine gas like zinc phosphide; causes respiratory tract irritation in animals (see Rodenticides).

b) Hydrogen cyanide (HCN): Toxicity due to cyanide.

c) Carbon disulfide ($CS_2$): Interferes with axon function by forming cross linking between neurofilaments; its inhalation causes pulmonary oedema, respiratory distress, convulsions, coma and death.

d) Sulfur dioxide ($SO_2$): It causes respiratory toxicity (see Air Pollutants).

**Organic Fumigants**:

a) Chloropicrin: Has very strong chlorine smell; its inhalation causes coughing and respiratory distress; irritant to eyes and also causes nausea and vomition.

b) Methyl bromide: Insecticidal fumigant also used in fire extinguishers. It causes neurotoxicity by inactivating –SH enzymes; its inhalation causes respiratory distress.

c) Ethylene dibromide: A soil fumigant; used to control soil worms. Inhalation causes pulmonary distress.

d) Dibromochloropropane (DBCP): It is a nematocidal fungicide fumigant. Its inhalation causes CNS depression and pulmonary oedema, and sterility in man (occupational exposure) as evident from low sperm counts.

warfarin & sweet clover vit K @ 2.5-5 mg/kg IV.

## 5. Rodenticides

**Causes**: Accidental ingestion of baits or poisoned rats (by pet animals) and malicious poisoning.

**Warfain and Congeners** (pindone, coumafuryl, coumachlor etc): Most commonly used, but potentially dangerous compounds.

**Mechanism of Toxicosis:** Anticoagulant rodenticides: Basic coumarin or indanedione nucleus: Act as anti-vitamin K and interfere with synthesis of coag. Factors I, II, VII, IX and X in liver and thus prevent conversion of prothrombin to thrombin resulting in failure of blood clotting – generalized haemorrhages.

**Clinical Signs**: Anaemia, hematomas, hemothorax, epistaxis and hematuria, weakness, ataxia, colic and polypnoea.

**Treatment**: Vitamin K1 @ 2.5 – 5 mg/kg iv or sc smallest possible needle at several locations to speed up absorption for 2 – 4 weeks. Fresh or frozen plasma @ 9 ml/kg or whole blood 20 ml/kg iv to replace clotting factors. Thoracocentesis to relieve dyspnoea due to hemothorax and artificial respiration with oxygen.

**Alpha Naphthyl Thiourea (ANTU)**:

**Mechanism of Toxicosis**: Causes massive pulmonary oedema. ANTU undergoes metabolism by microsomal mixed function oxidases releasing atomic sulfur which damages the endothelium of alveolar capillaries – leakage of fluid into alveoli – pulmonary oedema (pneumothorax). It causes vomiting on empty stomach due to intense local gastric irritation, but poisoning occurs if ANTU is ingested after feeding.

**Clinical Signs**: Moist rales, cyanosis, weakness, ataxia, rapid and weak pulse and subnormal temp.

**Treatment**: Gastric lavage, osmotic diuretics (mannitol), atropine (0.02-0.25 mg/kg sc) and keeping head inclined to facilitate drainage of fluids from lungs.

**Zinc Phosphide/Aluminum Phosphide**:

**Mechanism of Toxicosis**: Liberation of phosphine gas in acid pH in stomach – irritates GIT and causes CVS collapse.

**Clinical Signs**: Vomiting, acidosis, abdominal pain, aimless running, howling, ataxia, dyspnoea, gasping and convulsions.

**Treartment**: Calcium borogluconate and fluid therapy to reduce acidosis (2-4 litres of 5% soda bicarb. PO).

Red Squill: It is the ground bulbs of *Urgenia maritima*, contain cardiac glycoside, proscillaridin. Considered as the safest rodenticide (nontoxic to poultry, unpalatable to livestock, vomiting if cats/dogs ingest, rats are incapable of vomiting).

**Mechanism of Toxicosis**: Vomiting, ataxia, paralysis, dyspnoea, convulsions, depression, cardiac arrhythmia/failure.

**Treatment**: Gastric lavage/saline purgatives, atropine sc at 6-8 hr (prevent cardiac arrest).

**Sodium Monofluoroacetate**:

**Mechanism of Toxicosis**: Blocks cellular energy production by interfering with TCA. It is incorporated as fluoroacetyl coenzyme A in place of normal acetyl COA which condenses with oxaloacetate to form fluorocitrate – which causes inhibition of aconitase.

**Clinical Signs**: Nervousness, restlessness, depression, prostration, weak and rapid pulse, convulsions and death due to cardiac arrest.

**Treatment**: Emetics, gastric lavage, activated charcoal (0.5 gm/kg)

**Bromethalin**:
**Mechanism of Toxicosis**: Neurotoxin, uncouples oxidative phosphorylation in CNS. Increases CSF pressure – pressure on neurons/axons – impairment of impulse conduction – paralysis and death.
**Clinical Signs**: Vomiting, hyperexcitability, muscle tremors, convulsions, hind limb hyperflexia, posterior paralysis, depression, paralysis and death.
**Treatment**: Emetics, gastric lavage, and osmotic diuretics.

**Metaldehyde**: Also used as a **snail bait (molluscicide)**
**Mechanism of Toxicosis**: In stomach hydrolysed to acetaldehyde, which enters brain and reduces brain serotonin, norepinephrine and inhibitory transmitter GABA, causing excitation and hyper muscular activity
**Clinical Symptoms**: Nervous signs: Tremors, ataxia, rapid respirations and convulsions
**Treatment**: Emetics, gastric lavage, activated charcoal. Diazepam 2 – 5 mg iv. Lactate Ringer sol or 5 % glucose iv) to promote toxin excretion, combat dehydration and reduce acidosis induced by excessive muscular activity.

**Thallium Sulfate (Thallitoxicosis)**:
Generalized cellular toxicity. Dangerous. Affects GI, respiratory, bones/joints and nervous systems. Banned.
**Clinical Signs**: Haemorrhagic gastroenteritis, abdominal pain, dyspnoea, blindness, tremors and convulsions.
**Treatment**: Gastric lavagae with 1% sod. Iodide and 10% sod.iodide iv. Diethylthiocarbazone (dithiazone, 70 mg/kg, PO tid) within 24 hr and prussian blue 100 mg/kg bid as oral aqueous suspension to enhance thallium excretion in feces.

**Phosphorus**: Rarely used. Yellow and white P types (fire works/crackers) are toxic to all animals. Red P is nontoxic.
**Mechanism of Toxicosis**: Corrosive and protoplasmic poison: hepatotoxic.
**Clinical Signs**: Vomiting, diarrhoea (haemorrhagic), abdominal pain, jaundice, convulsions. Death due to hepatic and renal failure. Garlic odour of gastric contents. The vomitus glows in dark.
**Treatment**: 1% Cu $SO_4$ as emetic, forms nonabsorbable copper phosphide complex. Gastric lavage with 0.01-0.1% $KMnO_4$ or 0.2-0.4% $CuSO_4$ solution, followed by activated charcoal and 30 min later saline catharatic. Fat (favours P absorption) in diet should be avoided.

( activated charcoal, Barbiturates

**Strychnine (alkaloid of seeds of *Strychnos nuxvomica*)**: Convulsive poison. Violent death if ingested by pets. Once used as mammalicide (to kill stray dogs), but now banned as it causes violent death.
**Mechanism of Toxicosis**: Potent (convulsive) nervous poison. Antagonism of central inhibitory transmitters glycine and GABA.
**Clinical Signs:** Nervous signs (Excitement – tonic convulsion – depression – paralysis)
**Treatment:** Activated charcoal, anticonvulsants (barbiturates), gastric lavage with 2% aqueous tannic acid or dilute HCl or a 1:250 dilution of tincture iodine. Emetics are contraindicated. Gastric with sodium bicarbonate solution may increase absorption.

EXERCISE

1. Enlist the sources of pesticide toxicity in animals. Describe the mechanism of toxicosis, clinical signs, diagnosis and treatment of organochlorine insecticide toxicity in animals.
2. Enumerate the various sources/causes of insecticide poisoning in animals. Describe the mechanism of toxicosis, clinical signs, diagnosis and treatment of organophosphate insecticide toxicity in animals.
3. Give the classification of insecticides with examples. Discuss the toxicology of antiChE insecticides in animals.
4. Classify the insecticides with examples. Discus the toxicology of neurotoxic insecticides in animals.

5. Classify the agrochemicals having toxicity potential in animals. Describe the causes of pesticide toxicity in animals and what precautionary measures do you suggest to prevent pesticide toxicity in animals.
6. **Write short notes on the following**:
   a) Herbicide/Weedicide poisoning
   b) Rodenticide toxicity
   c) Carbamate insecticide toxicity
   d) Organochlorine insecticide toxicity
   e) Pyrethroid toxicity
   f) Phosphorus toxicity
   g) Thallitoxicosis
   h) Red squill
   i) ANTU
   j) Anticoagulant rodenticides
   k) Cyclodiene insecticide toxicity
   l) DDT
   m) AntiChE insecticide toxicity
   n) Amitraz
   o) Botanical insecticides
   p) Bipyridyl toxicity
7. **Describe the mechanism of toxicosis of the following**:
   a) Parathion
   b) Cypermethrin
   c) Carbaryl
   d) DDT
   e) Dieldrin
   f) Heptachlor
   g) Chloinated ethanes
   h) OP insecticides
   i) Carbamates
   j) ANTU
   k) Zinc phosphide
   l) Warfarin/Pindone
   m) Na fluoroacetate
   n) Na fluoroacetamide
   o) Methylfluoroacetate
   p) Bromethalin
   q) Metaldehyde
   r) Strychnine
   s) DNOC/DNP/DNBP
   t) Amitraz
   u) Diquat/Paraquat
   v) 2,4-D/2,4,5-T
   w) MCPB/MCPA
8. **Differentiate between the following**:
   a) Direct acting and indirect acting AntiChEs
   b) Malathion and carbaryl
   c) Parathion and DDT
   d) Parathion and 2-PAM
   e) Pesticide and insecticide
   f) Atropine and 2-PAM
   g) DDT and Dieldrin
   h) OPI toxicity and OCI toxicity
9. **Suggest the line of treatment of toxicity of the following**:
   a) Dichlorvos
   b) Methoxychlor
   c) BHC
   d) Propoxur
   e) Fenvalerate
   f) Warfarin/Pindone
   g) Strychnine
   h) Zinc phosphide
   i) Na fluoroacetate
10. **What do you mean by the following? Answer in one or two sentences for each. Give one example wherever necessary**:
    a) Delayed neurotoxicity
    b) AntiChE insecticide
    c) ChE reactivator
    d) Fumigant
    e) 2-PAM
    f) Weedicide
    g) Muscarinic blocker
    h) Antimetabolite
    i) Rodenticide
    j) Uncoupling of oxidative phosphorylation
    k) Red squill
    l) Phosphine
11. **What is the source of the following**:
    a) Nicotine
    b) Pyrethrum
    c) Proscillaridin
    d) Rotenone
    e) Derris
    f) Strychnine
    g) Red squill
12. **Matching** (parallel pairs):
    a) DDT/DDE: Chlorinated ethane
    b) Chlordane/Heptachlor: Cyclodiene
    c) Lindane/BHC: Hexachlorocyclohexane
    d) Diazinon: Organic phosphate
    e) Propuxor: Carbamate
    f) DFP: Direct ChE inhibition
    g) Parathion: Indirect ChE inhibition
    h) TOCP: Delayed neurotoxicity
    i) AChE inhibition: Muscarinic signs
    j) NtE inhibition: Delayed neurotoxicity
    k) OP Insceicides: Muscarnic signs
    l) Pyrethroids: Neurotoxicity
    m) OCI toxicity: Neurotoxicity
    n) Haloxon: NtE inhibition
    o) Coumaphos: ChE inhibition
    p) 2-PAM/DAM/MINA: ChE reactivator
    q) Fenthion: Indirect ChE inhibitor
    r) Dimethoate: Direct ChE inhibitor
    s) Tabun/Sarin: OP nerve gas
    t) Pyrolon/Isolan: Carbamate
    u) Methomyl: Carbamate
    v) Fenvalerate; Pyrethroid
    w) Rotenone: Natural insecticide
    x) DNOC/Paraquat: Herbicide
    y) Sulfur: Fungicide
    z) Thiram: Fungicide
    aa) ANTU: Rodenticide
    bb) 2,4-D/2,4,5-T: Weedicide
    cc) Warfarin; Hemorrhages
    dd) ANTU: Pulmonary oedema
    ee) Na fluoroacetate: Aconitase inhibition
    ff) Fluorocitrate: Antimetabolite
    gg) Strychnine: Convulsive poison
    hh) Red squill: Sea onion

ii) Red squill: Cardiac arrest
jj) 2,4-D/2,4,5-T: Uncouple oxid. phosphor.
kk) DNOC: Uncouple oxid. phosphorylation
ll) Metaldehyde; Mulluscicide
mm) Bordeaux mixture: Fungicide
ss) ANTU: Pulmonary oedema
tt) Fluoroacetate: Lethal synthesis
uu) Red squill: Cardiac arrest
vv) Red squill: Scilliroside
ww) Strychnine: Mammalicide
xx) Metaldehyde: Molluscicide
yy) Paraquat: Pulmonary toxicity
zz) Diaquat: GI and CNS toxicity
aaa) Aluminium phosphide: Phosphine gas
bbb) Captan/Folpet: Fungicide
nn) Warfarin/Pindone: Vitamin K
oo) Garlic odour: Phosphorus toxicity
pp) OCInsecticides: Mydriasis
qq) OPInsecticides: Miosis
rr) Zinc phosphide: GI irritation
ccc) Aluminium phosphide: Fumigant
ddd) $HCN/CS_2/SO_2$: Fumigant
eee) Chloropicrin: Fumigant
fff) Methyl bromide: Fumigant
ggg) DBCP: Fumigant
hhh) Ethylene dibromide: Soil fumigant
iii) DBCP: Nematocidal/Fungicide/Fumigant
jjj) Phosphorus: Garlic odour/Vomitus glows in dark

13. **Write the full form of the following**:

a) DDT
b) DDD
c) γBHC
d) AchE
e) TOCP
f) DFP
g) NtE
h) 2,4-D
i) 2,4,5-T
j) ANTU
k) 2-PAM
l) DAM
m) MINA
n) DNP
o) PCP
p) DNOC
q) DNBP
r) MCPB
s) MCPA

14. **Substantiate each of the following statements by giving the most appropriate reason/explanation in one two sentences**:

a) OPI toxicity in animals is characterized by muscarinic and nicotinic signs.
b) DDT toxicity in animals is characterized by nervous signs.
c) Pyrethroids cause neurotoxicity.
d) Cyclodiene insecticides cause neurotoxicity.
e) Parathion, malathion, fenthion and fenitrothion are called as indirect acting antiChEs.
f) Dichlorvos, diazinon, dimethoate, DFP and TEPP are called direct acting antiChEs.
g) OPIs have more acute toxicity potential than carbamate insecticides.
h) The use of OCIs as ectoparasiticides is on the decline.
i) DFP/TOCP causes delayed neurotoxicity.
j) Atropine is the specific antagonist in treating acute OPI/carbamate insecticide toxicity.
k) 2-PAM/DAM/MINA reverses acute OPI intoxication.
l) ChE reactivators are not to be used in acute carbamate insecticide toxicity.
m) Saline purgatives, but not the oil purgatives are used in treating acute insecticide toxicity.
n) Chlorophenoxy herbicides (2,4-D or 2,4,5-T) aggravate nitrate and cyanogenic plant toxicity.
o) DNP/DNOC or chlorophenol herbicides prevent ATP formation
p) Paraquat causes pulmonary toxicity.
q) Dinitrophenols (DNP, DNBP and DNOC) are called broad spectrum pesticides.
r) Chlorophenols (pentachlorophenol) deplete energy stores.
s) Thallium toxicity is due to inactivation of succinic dehydrogenase, MAO and cathepsin.
t) Acute zinc phosphide toxicity in dogs is due to severe gastroenteritis.
u) Zinc phosphie is highly toxic if ingested with the bait.
v) Warfarin/pindone toxicity is characterized by internal organ haemorrhages.
w) Vitamin K is the antidote of warfarin/pindone toxicity.
x) Acute ANTU intoxication is characterized by respiratory distress.
y) The mode of action of Na fluoroacetate/Na fluoroacetamide involves formation of false metabolite.
z) Na fluoroacetate/Na fluoroacetamide interfere with Kreb's cycle.
aa) Na fluoroacetate/Na fluoroacetamide prevent cellular energy production.
bb) Bromethalin causes toxicity signs characterized by nervous excitability.
cc) Strychine causes violent death.
dd) Req squill is a botanical rodenticide
ee) Strychnine is no longer regarded or used as a safe rodenticide.
ff) Red squill is considered as one of the safest rodenticides.
gg) Red squill exerts rodenticide action through cardiac arrest.
hh) Red squill is selectively toxic to rats.
kk) )CIs cause neuronal hyperexcitability
ll) Norbromide can also be considered as one of the safest rodenticides.
mm) ANTU causes pulmonary toxicity
nn) DBCP causes sterility
mm) Cholinergic signs are noticed in acute OP or carbamate insecticide toxicity.
pp) Fumigants as insecticides are advantageous over the conventional insecticides.

# CHAPTER – 47: PLANT POISONING

## 1. Cyanogenetic Plant Poisoning (HCN/CN)

Poisoning in grazing livestock resulting from ingestion of plants containing hydrocyanic acid (HCN) or the cyanogenic glycosides is called cyanogenic/ cyanogenetic plant poisoning. The toxicity of such plants is due to cyanide (CN). In plants CN is present in two forms: a free HCN and a bound form as a cyanogenic glycoside (CG). Free HCN is liberated from the glycoside by the hydrolyzing enzymes of the ruminal or intestinal microflora or by a hydrolyzing enzyme (ß - glycosidase) present in the same plant or in other plants.

Ruminants are most susceptible species. Sheep and goats are less susceptible as compared to cattle or buffaloes (differences in the enzymes of fore stomachs). Pig and horse are relatively resistant to cyanogenic plant poisoning due to destruction of the hydrolyzing enzyme by gastric acidity (less of free HCN is released).

**Factors affecting cyanogenic plant poisoning:**

1. Species variation (see above).
2. Stage of growth of plants: Young, immature plants or rapidly growing plants especially after a period of drought are highly toxic (more HCN or the CG). Wilted/trampled or frost bitten plants are more toxic (ready liberation of free HCN). Rapidly growing parts of a plant contain more HCN than the older parts: Young/tender leaves or pods of *Acacia leucophloea* more toxic than the mature/old leaves or pods (more HCN and CG).
3. During drought conditions the plants have more HCN or CG.
4. Nitrate fertilization or application of weedicides (2,4 – D) increases HCN in plants
5. Drying or ensiling of the plants lowers HCN content.

Plant material containing 20 mg of HCN per 100 gm is toxic to livestock. The oral minimum LD of KCN in almost all animals = 2 mg/kg.

**Cyanogenic plants (Glycoside)**: *Sorghum vulgare* and other spp. (Dhurrin), *Linum usitatisimum* (Linamarin), *Lotus* spp. (Lotustralin or lotusin), Bitter almonds: *Amygdalus communis* (amygdalin), *Acacia leucophloea, Prunus* spp. *Andrachne cordifclia, Neyraudia medagascariensis.*

HCN is rapidly absorbed from GIT or from lungs through inhalation. In liver it is rapidly detoxified to thiocyanate by rhodanese enzyme, which is excreted through urine. Some HCN is also excreted through exhaled air giving a characteristic bitter almonds smell to the expired air. However, if excess HCN is liberated it is absorbed resulting in toxicity.

**Mechanism of Toxicosis**: The cause of death in cyanide toxicity is cytotoxic anoxia. The CN ion has great affinity to Ferric ion of Cytochrome Oxidase, an important enzyme in the respiratory chain responsible for utilization of oxygen for cellular oxidative reactions and energy production. Therefore, the cyanide ion by forming a complex inactivates the enzyme (cyan-cytochrome oxidase). Oxygen is not exchanged for cellular metabolic reactions and it is retained in the blood (bright red color). Though oxygen is there it is not being used, thus resembling a condition "lack of oxygen" – anoxia. Therefore, the cells die. Cell death due to anoxia.

**Clinical Signs**: In most of the cases the poisoning has been of **acute** in nature. If large quantities of the cyanogenic plant are ingested, the animals die within 30 min of ingestion. If death is prolonged the animals show: anxiety, restlessness, bright red mucosae (in the beginning), staggering gait, muscular tremors, weak and rapid pulse, recumbency, bloat, respiratory distress, opisthotonus, terminal convulsions, cyanotic mucosae (in terminal stages) and death (resp. failure)

**PM Changes**: Congestion/haemorrhages in abomasum, small intestines, trachea, lungs and heart. Bright red unclotted blood. Bitter almond smell of ruminal/intestinal contents. Send plant/ruminal contents for chemical analysis (after feezing). If PM is delayed send skeletal muscle pieces in 1% mercuric chloride sol for analysis of cyanide.
**Diagnosis**: History, sudden death, anoxic syndrome and color of mucosae suggest HCN or cyanogenic plant poisoning. Confirmation by subjecting the plant material or ruminal contents to sodium-picrate paper test.

**Treatment**: Specific Antidotal Therapy: Administration of sodium nitrite and sodium thiosulfate.
Sodium nitrite + Haemoglobin ($Fe^{++}$) → Methaemoglobin ($Fe^{+++}$)
Cytochrome ($Fe^{+++}$)-Cn complex + Met Hb → CyanmetHb + Cytochrome oxidase
Sodium thiosulfate + CyanmetHb → Thiocyanate + Haemoglobin + Sodium sulfate
Thiocyanate is the nontoxic form of cyanide, which is readily excreted through kidney.
Sodium nitrite being a (direct) vasodilator promotes blood supply to the vital organs.
Cattle or Buffaloes: Sodium nitrite 3 G and sodium thiosulfate 15 G in 200 ml DW i/v
Sheep, goat or calves: Sodium nitrite 1 G, Sodium thiosulfate 2.5 G in 50 ml DW i/v
Repeat, with caution, depending upon the condition of the animal
Other Treatment: Artificial respiration/analeptics, symptomatic treatment to relieve bloat etc.

## 2. Photosensitization

It is an abnormal dermal reaction that appears in lightly pigmented or unpigmented skin areas of the animals due to UV activation of the photodynamic substance present in the peripheral circulation. The reaction is characterized by development of dermatitis, intense pruritis/itching, swelling, and secondary bacterial infections, if not treated ends up with gangrene and sloughing off of the affected areas.
The syndrome is observed in body areas (skin) which are exposed to the direct sun light such as head, face, nose, mandibular area, ears and cornea in sheep/goat and udder, teats and muzzle and lightly pigmented areas over thorax or abdomen in cattle and buffaloes.

The reaction occurs within a few hr to few days of exposure to bright sunlight following ingestion of the culprit plant or drug (depending upon the amount of photodynamic agent that enters into the peripheral circulation). Hepatotoxicity predisposes the grazing livestock to photosensitization. Therefore, in livestock photosensitization invariably involves a **triad of events**: hepatic disease, ingestion of fresh green fodder and exposure to bright sun light. All the species (even the man is not free) are sensitive, but dark or black-skinned animals and those confined to closed quarters are not affected.

Basing on etiology photosensitization has been categorized into three types namely: Primary, secondary or inherited photosensitization. The first two types are commonly encountered in animals.
**Primary Photosensitization:** It is due to entry (ingestion or by any other means) of a photodynamic agent into the body. Such agents are inherently photodynamic/photosensitive (get activated by UV radiation of 400 nm). They are mainly of plant origin from livestock point of view. Certain chemicals, drugs or their metabolites, are also inherently photosensitive.
Some plants causing primary photosensitization (photodynamic principle) are:
*Parthenium hysterophorus* (Parthenin), *Fagopyrum esculentum* (Fagopyrin), *Hypericum perforatum* (Hypericin, it also has antidepressant (MAO inhibition), anti-inflammatory and germicidal actions).
Chemicals (Dyes): Acridine and rose bengal.
Drugs: Phenothiazine (Sheep: Phenothiazone sulfoxide: Photosensitization keratitis)

**Secondary Photosensitization:** It is a consequence of liver disease (hepatitis): swollen hepatocytes → microobstruction of intrahepatic biliary ductules → obstruction of common/hepatic bile duct → blockade of secretion of bile into intestines. It is therefore secondary to liver pathology. It is of plant origin. Normally chlorophyll, the photosynthetic pigment of plants, ingested through green grasses by the livestock is

metabolized to phylloerythrin (photodynamic) which is carried by bile into intestines and excreted through faeces. However, due to obstruction of bile ducts/flow (above) phylloerythrin is not excreted and it enters blood and leaks into peripheral circulation. All the hepatotoxic plants are thus expected to cause secondary photosensitization. Some examples of plants causing hepatotoxicity and secondary photosensitization are:

*Agave sisalana* *Lantana camara* *Shobia arabeca*
*Lupinus augustifolium* *Senecio jacobaeum* *Tribulus terrestris etc.*

In addition all the drugs or chemicals ($CCl_4$) causing liver damage are expected to cause secondary photosensitization in grazing or greens fed livestock.

**Inherited or Congenital Photosensitization**: The exact etiology is not established. It may be due to congenital prophyrias (abnormal biosynthesis of porphyrins) causing excessive production of bilirubin and failure of its excretion (jaundice). The condition has been linked to blockade of heme biosynthesis, where several reactions involving the enzymes such as uroporphyrinogen decarboxylase, coproporphyrinogen oxidase, protoporphyrinogen oxidase and ferrochelatase are blocked resulting in accumulation of porphyrinogens. The porphyrinogens are oxidized to derivatives which are highly photosensive. Thus, porphyrinogen accumulation as a result of inhibition of heme synthesis and subsequent formation of photosensitive porphyrinogen derivatives is considered the cause of congenital photosensitization.

**Genesis of photosentitization reaction or syndrome :** In all the three types the genesis of photodynamic reaction or photodynamic syndrome is almost similar, though the causes are different as explained above. The mechanism is explained as follows. The photosensitive or photodynamic agent while in peripheral circulation in the specific skin areas (as above mentioned) gets excited or activated by the ultra violet radiation of a specific wave length (< 400 nm) and combines with molecular oxygen to form oxygen radicals. These oxygen free radicals injure or lyse the lysosomal membrane releasing the destructive lysosomal enzymes into the cytoplasm of the cells and eventually causing necrosis of the tissues underlying the skin. Histamine is released in the damaged tissues causing local reactions in the skin such as intense itching/pruritis, erythema, oedema, oozing serous fluid and pain. The affected skin areas become highly sensitive to secondary bacterial infections. If not treated gangrene sets in with sloughing of the affected skin areas.

**Clinical signs**: The dermal signs start with erythema, itching,oedema (swelling) and irritation. Serous fluid oozes from the area due to rubbing against fixed objects. Necrosis, gangrene and exfoliation or sloughing of the superficial skin layers. The swollen mandibular area (oedematous) in sheep looks like bottle jaw and the head looks big (big head syndrome). Conjunctivitis and lacrimation (watery to thick) in cattle. In sheep blindness may result due to corneal clouding/opacity. In hepatogenous type there is jaundice. In congenital type increased excretion of porphyrins in urine (porphyrinuria: reddish-brown urine)

**Diagnosis**: Jaundice, cutaneous lesions, history of suspected plants in the area or their ingestion, elevated serum phylloerythrin levels and porphyrins in urine suggest photosensitization.

**Treatment**: Keep the animals protected from UV radiation for 5-7 days (sun screens or dark rooms). Carbohydrate rich diet with ß-carotene supplementation (reduces free radical formation). Topical treatment for dermatitis: Demulscents, antibiotics, antihistamines. Administration of liver tonics.

### 3. Other Common Plant Toxicities

***Abrus precatorius*** (Sui Posoning): Used for malicious killing of animals.

The seeds of *A. precatorious* (used as beads in jewellary/ornaments; also known as rosary pea, precatory bean, jequirity bean or carb's eye) contain a toxalbumin abrin which is one of the most poisonous phytotoxins (i/v median lethal dose in mice = 0.1 µ g/kg). The whole seeds when ingested are not toxic (except in poultry). The powder of the seeds is toxic in all species (ruminants, horses and man). Powder of one seed can kill a small child or medium sized dog and 60 G seed powder can kill a horse. Needles/spikes/ nails etc coated with the paste of crushed seeds and inserted into the body cavities or under the skin (sui poisoning) are used for malicious killing of cattle. Animals die within 2-4 days after exhibiting salivation, stiffness of joints, ataxia, incoordination, muscular spasms, hyperthermia and convulsions, with extremely painful swelling at the site of implant. Congestion of visceral organs and petechial hemorrhages through out the body are seen on PM. Abrin acts as a proteolytic enzyme and

causes agglutination of RBC (binds to glycoproteins of the RBC membranes – bridges between the cells). Abrin due to its peculiar binding potential is also selectively transported by the nerves. No specific antidote. Remove the source (from GIT by emesis, gastric lavage, demulcents, saline purgatives etc) and i/v infusion of fluids and electrolytes.

***Calotropis procera/gigantea:*** Used for malicious killing of animals. A shrub usually found on the boundaries of crop fields and in waste lands. All parts of plant are toxic. The plant is not palatable, hence not usually eaten by the animals. The toxic principles are cardiotoxic glycosides calotroxin, calactin, gigantin, uscharin. The latex is an irritant to skin and mucous membranes, if placed in eye causes conjunctivitis and extreme cases blindness. Following oral ingestion its leaves or fruit cause severe gastroenteritis and **cardiac arrhythmia** and death is due **cardiac arrest.**

***Datura straminium (Thorn appel; D. alba/metel):*** It is a common shrub found widely growing in waste lands. The plant has strong unpleasant odour and hence not usually eaten by the grazing livestock. All parts of the plant are toxic. The toxic principles are anticholinergic (antimuscarinic) alkaloids: Atropine, hyoscyamine and scopolamine. The toxicity is characterized by anticholinergic signs (dryness of mouth, mydriasis and disturbed vision, ruminal atony, restlessness, hyperpnoea, tachycardia, muscular spasms, and nervous signs and death is due to cardiac arrest. Herbivores are more susceptible than the carnivores. Rabbit is resistant to atropine toxicity, due to presence of atropinase enzyme in liver which destroys (hydrolyzes) and inactivates the toxic alkaloid. Treatment is symptomatic. Pharmacological antagonists of atropine like physostigmine can be used with caution. The other plants containing atropine and related alkaloids are *Atropa belladonna, Hyoscyamus niger* and *H. muticus* .

***Ipomoea carnea*** (Besharm): It is a large shrub commonly found in water logging waste lands and along sides of canals and is also grown as a hedge. Ingestion of leaves causes toxicity in goat, sheep and calves. Goats are most susceptible species. Subacute toxicity is the common form, characterized by salivation, diarrhoea, anaemia (normocytic-hypochromic), enhanced erythrocyte fragility, haematuria, liver damage, muscular spasms, incoordination, staggering gait, paralysis of hind limbs, recumbency and death. The exact nature of toxic principles is not known. The plant contains lysergic acid alkaloids, a resinous cathartic and saponins. Treatment is symptomatic: Haematinics, nervine tonics, hepatic tonics etc.

***Lantana camara:*** Secondary (hepatogenous) photosensitization. It is a very hardy shrub and is one of the most toxic weeds found throughout the country, hills and plains. There are several varieties (distinguished by the colour of flowers), the red variety is considered most toxic. Ingestion of leaves is the cause of toxicity. Grazing livestock normally do not eat the plant due to very pungent odour. The toxic principles are hepatotoxic triterpene lantadenes A and B. The toxicity is characterized by hepatotoxicity, cholestasis and photosensitization. The details are dealt under photosensitization.

***Nerium oleander, N. indica*** (Kaner): These are medium shrubs, mainly grown as an ornamental plant. Poisoning occurs by ingesting (scarcity periods) the leaves or pods (seeds). Toxicity is mainly due to presence of cardiotoxic digitalis- like glycosides: oleandroside, nerioside, oleandrin, neriodrin and nerioderin. The plants also have alkaloids pseudocurarine, neriene and neriantine. Poisoning is of acute type and death results from failure of contraction of myocardium (by interfering with $Na^+$ - $K^+$ - dependent ATPase system and paralysis of sympathetic nerve supply to heart).The leaves/pods/seeds also cause intense gastroenteritis.

The toxicity signs are vomiting, abdominal pain, diarrhoea, tenesmus, cardiac arrhythmia (bradycardia, premature systoles, tachycardia, heart block), labourded breathing, muscular tremors, convulsions, paralysis and death. Milk from poisoned cows may also cause toxicity in man (salivation, vomiting, diarrhoea, muscular weakness, visual difficulty and even convulsions) Treatment is symptomatic. Remove the source and reduce the absorption (emetics: apomorphine, osmotic or saline purgatives, gastric lavage

and demulcents). Administer atropine along with propranolol, sedatives/tranquilizers etc. Infusion of calcium containing fluids is contraindicated (aggravates cardiac arrhythmia). The seeds of yellow oleander *Thevetia peruviana* or *Cerebera thevetia* are highly poisonous to both man and animals (used for malicious killing of animals and for homicide purpose). They contain cardiotoxic glycosides thevetin and cereberin causes toxicity similar to *N. oleander.*

***Parthenium hysterophorus*** (Gajar ghaas): The most problematic weed. Entered in our country as a contaminant of wheat gifted by USA in early sixties. First appeared in Pune (MH) from where it spread like wildfire throughout the country, posing a serious agricultural (severe crop losses due to its uncontrollable growth in farm fields: A very hardy plant) and public health problem.
Toxicity (Health hazards): Allergic contact dermatitis in farm labourers and grazing livestock (buffaloes), Liver damage in animals following long term ingestion. Contains a photodynamic agent a sesquiterpene lactone Parthenin (causes primary photosensitization). Milk from *Parthenium* ingested cows or buffaloes is bitter in taste.
Treatment: Shifting of animals to normal fodder. Symptomatic treatment of dermatitis: Antipruritics, antibiotics, antihistamines etc. Tonics to rejuvenate the damaged liver.

***Pteridium aquilinum:*** Bracken fern poisoning: Ferns are found in the hilly tracts. The ferns are normally avoided by the grazing livestock, but ingest them during scarcity periods. The animals may develop a taste for ferns. The whole plant, including the rhizome is poisonous. The toxic principle in bracken fern are a thiminase, a carcinogenic glycoside (ptaquiloside) and a aplastic anaemia factor. Its toxicity is different in ruminants and nonruminants (horses and pigs). In nonruminants the toxicity is mainly due to thiaminase activity → thiamine ($B_1$) deficiency (the enzyme thiaminase acts by splitting the vitamin to thiazole and pyrimidine). In ruminants toxicity is not due to antithiamine action, but is due to an acute haemorrhagic syndrome → thrombocytopaenia (increase in blood clotting time), depression of haematopoiesis (erythrocytopaenia and leucopaenia) and tumors in urinary bladder. The clinical signs in nonruminants are incordination, staggering, muscular tremors, generalized congestion and serosal and mucosal haemorrhages in horses; vomiting, constipation and retarded growth in pigs. In ruminants the clinical signs are blood in faeces, haematuria, ruminal atony, watery discharge from eyes and nostrils and laboured respiration
Treatment in cattle: Thiamine is of no use in ruminants. Most effective is blood transfusion (0.4 L in young animals and in adult animals 1 – 4 L blood with 3% Na citrate followed by a second transfusion of half the above quantity) together with single i/v injection of 10 ml of 1% protamine sulfate to counteract the anticoagulant effect of released heparin and administration of D,L-batyl alcohol (erythropoietic-bone marrow stimulant) 1 G in 10 ml olive oil s/c for five consecutive days in early stages of poisoning. Treatment in horses and pigs consists of administration of thiamine (100 mg s/c once or twice a day till clinical signs disappear).

***Ricinus communis*** (castor bean): Used for malicious killing of animals.
Seeds contain 56% oil – castor oil and 26% proteins. The pomace or castor cake (residue left after oil extraction of the seeds) contains the phytotoxin ricins: ricin I and ricin II (lectins absorbed from GIT). Ricin II is more toxic than ricin I. Poisoning results from accidental ingestion or deliberate feeding of cake. All animals are sensitive, but horses are the most susceptible species. Ricin induces hydrolytic fragmentation of ribosomes and their inactivation and thus inhibits protein synthesis. Ricin also damages GI mucosa (impairs digestion and absorption of nutrients), hepatocytes (liver damage) and renal tubules (nephrosis). A characteristic latent period (2-3 days) between ingestion of castor beans or cake and the onset of clinical signs. Horses show incoordination, profuse sweating, muscular spasms and tumultuous heart (beating with such force shaking the entire body). All animals show profuse watery diarrhoea, icterus, colic, oliguria, prostration, convulsions and death. Animals may develop immunity by injection of the toxin in gradual increasing doses. Cattle become immune by feeding the increasing amounts of the bean. The solutions of

the toxin become nontoxic, but retain immunogenic properties by heating (coagulation). Treatment consists of giving antiserum (from previously hyperimmunized animal). Removal of the poison (gastric lavage and saline purgatives). Fluid and electrolyte therapy, saline diuretics and urinary alkalizers.

***Strychnos nuxvomica:*** Nuxvomica poisoning. Nuxvomica plant poisoning in livestock is rare and it occurs due to ingestion of seeds of the plant. The main toxic principle of the seeds is strychnine (also contain another alkaloid brucine), a convulsive alkaloidal poison (powerful spinal stimulant, also contains another alkaloid brcine). It was once used to kill the stray dogs and as a rodenticide. Now it is prohibited to use strychnine to kill the stray dogs (causes violent and painful death) and as rodenticide also it is replaced by safer compounds (from animal toxicity and public health points of view). Its seed powder (pulvis nuxvomica) is recommended as a bitter stomachic in ruminants under indigenous system of medicine (not in dogs – causes toxicity). Strychnine toxicity is always acute, characterized by violent tonic convulsions followed by paralysis of respiratory muscles and death. Its CNS stimulant activity is due to competitive antagonism of inhibitory transmitter glycine (blockade of postsynaptic inhibition motoneutons and interneurons in spinal cord) resulting in uncontrolled excitation of spinal reflex, stimulation of extensor muscles and tonic seizures. Treatment of toxicity is symptomatic: Anticonvulsants and central muscle relaxants. Diazepam mimics glycine and counteracts the action of strychnine. Use of morphine or ketamine is contraindicated (aggravate convulsions). General antidotes to neutralize the alkaloidal poisons may also be useful in reducing the absorption of strychnine from the GIT.

***Argemone mexicana:*** It is a weed found in the crop fields. The seeds resemble mustard seeds and hence are the adulterant of mustard. The seeds contain an oil argemone oil (adulterant of mustard oil), ingestion of which causes dropsy (SC oedema of extremities), cardiomyopathy and glaucoma in human beings. The toxic principle of the oil is an alkaloid sanguinarine (isoquinoline alkaloid); toxic to poultry and ruminants. Seeds as a contaminant of wheat, when ingested by poultry cause decreased egg production, oedema, depression, ataxia, cyanosis of the comb, hemorrhagic enteritis and death. Treatment is symptomatic.

### 3. Miscellaneous Toxic Plants:

| Sr.No. | Plant | Toxicological Properties |
|---|---|---|
| 1 | *Veratrum alba, V. californicum, V. viride* | Teratogenic in sheep: malformed lambs (Cyclops, anophthamia or microopthalmia). Presence of teratogenic cyclopamine. |
| 2 | *Melilotus alba, M. officinalis* | Sweet clover poisoning; anticoagulant toxicity, The hay contains coumarin, which under favorable conditions (spoilage/mold infestation) gets converted to dicoumarol which exerts anticoaguiant action. Dicoumarol exerts antithrombin acion like warfarin (see Rodenticides) causing by internal haemorrhages. |
| 3 | *Allium cepa* (Onion) | Toxic to cattle, sheep horse and dog. Contains an oxidant N-propyl disulfide which inhibits erythrocyte glucose-6-phosphate dehydrogenase causing hemolysis; causes hemolytic anaemia, hemoglobinuria and degenerative changes in kidney. |
| 4 | *Ipomoea batatus* (Sweet potato) | Mold infested tubers are toxic to ruminants; contain pneumotoxic furanoterpenes; cause pulmonary oedema and dyspnoea. |
| 5 | *Jatropha curcas* (Ratanjyot) | Toxic to ruminants and horses; contain a drastic purgative jatrophin; causes hemorrhagic gastroenteritis and severe diarrhea. |
| 6 | *Tribulus terrestris* | Toxic to sheep and goat; contains saponins causing hepatogenous photosensitization and beta-carboline alkaloids causing posterior rigidity. |
| 7 | *Glycine max* (Soybean) *Medicago sativa* (alfalfa, lucerne), *Trifolium repens* (white clover) | Contain phytooestrogens (coumestans/isoflavones). Soybean affects pigs, Alfalfa/lucerne affects cattle/sheep. *T. repens* affects sheep. Reversible flock infertility, oestrus prolongation and oestrogenic effects, |

## EXERCISE

1. Describe source, mechanism of toxicosis, clinical signs, diagnosis and treatment of cynagenetic plant poisoning in livestock.
2. Mention the major cyanogenic glycosides along with their source. Describe the various factors that determine cyanogenic plant poisoning in livestock.
3. Describe biochemical basis of toxicosis and treatment of cyanide poisoning in livestock.
4. What is photosensitization? Describe the various types and line of treatment of photosensitized animals.
5. List any four important toxic plants of your locality/region, mention their toxic principles and write in brief of their mechanism of toxicosis along with clinical signs and treatment of their poisoning.
6. **Write short notes on the following**:
   a) Biochemical basis of cytotoxicity of cyanide.
   b) Biochemical basis of treatment of cyanide toxicity
   c) Factors altering HCN content in plants.
   d) Cyanogenic glucosides/glycosides.
   e) Teratogenic plants.
   f) Oxalate poisoning.
   g) Primary photosensitization
   h) Secondary photosensitization.
   i) Photosensitization reaction.
   j) Anticoagulant plant toxicity.
   k) Plants causing thiamine deficiency.
   l) *Lantana* poisoning.
   m) Kaner poisoning.
   n) Sui poisoning.
   r) Nuxvomica poisoning.
   o) *Ipomoea carnea* poisoning.
   s) *Calotropis* poisoning.
   p) Baracken fern poisoning.
   t) *Nerium* poisoning.
   q) Castor bean poisoning.
   u) Datura poisoning.
7. **Differentiate between the following**:
   a) Free HCN and Bound HCN
   b) Haemoglobin and methaemoglobin
   c) Chlorophyll and phylloerythrin
   d) HCN and Dhurrin
   e) Anoxia and Hypoxia
   f) Cyanide toxicity and Nitrite toxicity
   g) Primary photosensitization and Secondary photosensitization
8. **Write the mechanism of toxicosis of the following**:
   a) Cyanide/HCN
   b) Dhurrin/Linamarin
   c) Parthenin/Hypericin/Fagopyrin
   d) Lantadenes
   e) Abrin
   f) Ricin
   g) Oleandroside/Nerioside
   h) Calotropin/Thevetin
   i) Strychnine
9. **Give the line of treatment of the following poisonings**:
   a) Cynanogenic plants/Cyanide
   b) Lantana
   c) Datura
   d) Castor bean
   e) Nuxvomica
   f) Bracken fern
   g) Photosensitization
10. **Mention the toxic or active principle (s) of the following plants**:
    *a) Sorghum vulgare*
    *b) Linum usitatisimum*
    c) Bitter almonds
    d) Lotus plant
    *e) Prunus spp.*
    *f) Acacia leucophloea*
    *g) Strychnos nuxvomica*
    *h) Parthenium hysterophorus*
    *i) Lantana camara*
    *j) Fagopyrum esculentum*
    *k)* Sweet clover
    *l) Hypericum perforatum*
    *m) Abrus precatorius*
    *n) Calotropis gigantea/procera*
    *o) Datura alba/stramonium/metel*
    *p) Veratrum viride/alba*
    *q) Nerium oleander*
    *r) Cerebera thevitea*
    *s) Pteridium aquilinum*
    *t) Ricinus communis*
    *u) Melilotus officinalis/alba*
11. **Write the source of the following (name of the plant)**:
    a) Dhurrin
    b) Linamarin
    c) Strychnine
    d) Brucine
    e) Atropine
    f) Abrin
    g) Ricin
    h) Calotropin
    i) Gigantin
    j) Nerioside
    k) Oleandroside
    l) Cereberin
    m) Thevetin
    n) Ptaquiloside
    o) Thiaminase
    p) Lantadenes
    q) Fagopyrin
    r) Parthenin
    s) Hypericin
    t) Coumarin
    u) Aplastic anaemia factor
    v) Teratogenic principles

12. **What do you mean by the following? Answer in one or two sentences for each.**
    a) Cyanogenic glycoside
    b) Bound HCN
    c) Phylloerythrin
    d) Abrin
    e) Ricin
    f) Sui poisoning
    g) Teratogenic plant
    h) Anticoagulant plant
    i) Antithiamine plant
    j) Adulterant of mustard seeds
    k) Dhurrin
    l) Linamarin
    m) Sweet clover
    n) Bracken fern
    o) Hypericin
    p) Parthenin
    q) Cytochrome oxidase
    r) Congenital porphyria

13. **Give two examples (names) of the following:**
    a) Nitrate rich plants
    b) Selenium rich plants
    c) Oxalate rich plants
    d) Teratogenic plants
    e) Hepatotoxic plants
    f) Plants causing delay in clotting time
    g) Cardiotoxic plants
    h) Cyanogenic plants

14. **Matching** (parallel pairs).
    a) *Sorghum vulgare*: Dhurrin
    b) Linseed plant: Linamarin
    c) Bitter almonds: Amygdalin
    d) *Lotus* spp. Lotustralin/lotusin
    e) Photodynamic: Parthenin/Hypericin
    f) Sui poisoning: *Abrus precatorius*
    g) Atropine: *Datura* spp.
    h) *Nerium* spp.: Cardiotoxic
    i) Abrin: Toxalbumin
    j) Ricin: Lectin/Toxalbumin
    k) Teratogenic: *Veratrum* spp.
    l) Haemorrhages: Sweet clover
    m) *Beta oxalis*: Oxalate rich plant
    n) *Euphorbia* spp.: Nitrate rich plant
    o) HCN: Cytotoxic anoxia
    p) Nitrate rich plants: Hypoxia
    q) Oxalate rich plants: Renal injury
    r) Thorn apple: *Datura stramonium*
    s) Rosary pea: *Abrus precatorius*
    t) Crab's eye: *Abrus precatorius*
    u) *Allium cepa*/Onion: Haemolytic
    v) *Astragalus* spp.: Selenium rich plant
    w) Sweet clover: *Melilotus alba/ officinalis*
    x) Abrin: Phytotoxin
    y) Ricin: Phytotoxin
    z) Ptaquiloside: Carcinogenic glycoside
    aa) Brucine: *Strychnos nuxvomica*
    bb) Argemone seeds: Pulmonary/SC oedema/Anasarca
    cc) *Pteridium aquilinum*: Thiaminase/Bracken fern
    dd) Primary photosensitization: *Hypericum perforatum*
    ee) Phytooestrogens: *Glycine max/Medicago sativa/Trifolium repens*
    ff) Secondary photosensitization: *Lantana camara*

15. **Substantiate the following statements, by giving the most appropriate reason in one or two sentences:**
    a) Cyanide causes cytotoxic anoxa.
    b) Horses/pigs are less susceptible to cyanogenic plant toxicity as compared to cattle.
    c) Methaemoglobin has toxicological as well as therapeutic significance.
    d) In cyanide poisoning mucosae are bright red in initial stages and cyanotic in terminal stage.
    e) Very young shoots of jowar are highly toxic.
    f) Blindness may occur in photosensitized animals.
    g) Phenothiazine treated animals should be kept in doors.
    h) Hepatogenous photosensitization is called secondary photosensitization.
    i) Fagopyrin-induced photosensitization s called primary photosensitization.
    j) *Lantana*-induced photosensitization is called secondary photosensitization.
    k) Phenothiazine causes primary photosensitization.
    l) Mold infested sweet clover becomes highly toxic.
    m) *Abrus precatorius* poisoning is called *sui*(needle) poisoning.
    n) Oleander/Calotropin poisoning results in death due to cardiac arrest.
    o) *Sorghum* during early growth following nitrate fertilization or treatment with 2,4-D or 2,4,5-T is highly toxic.
    p) Cyanogenic plans. during drought are highly toxic.
    q) Retarded (in growth) cyanogenic plants are highly toxic.
    r) Hepatic disease predisposes grazing livestock to photosensitization.
    s) Rabbit is resistant to *Datura* poisoning.
    t) In ruminants bracken fern toxicity is characterized by haemorrhagic syndrome.
    u) In cattle thiamine is of no value in treating bracken fern poisoning.

# CHAPTER – 48: TOXINS

## 1. Mycotoxins

The mycotoxins are metabolites produced by the pathogenic micro-fungi (Macro fungi – mushrooms: mushroom poisoning does not come under mycotoxicosis). The fungi grow on feeds: Grasses, grains, oil seed cakes etc. under favourable conditions (warm, humid and moist) i.e. Temperature: 25-32 $^{o}$ C, relative humidity: 90 – 95 % and moisture > 15 %

**Classification of Mycotoxins**: Based on their pathogenecity

Hepatotoxic: Aflatoxins, rubratoxins.
Nephrotoxic: Ochratoxin, citrinin
Neurotoxins: Penitrem, patulin, citreoviridin, ergotoxins
Toxins causing lameness: Ergotoxins
Oestrogenic toxin: Zearalenone
Histaminergic toxins: Slaframine, ergotoxins

### Aflatoxins

These toxins are produced by the fungi of Genus *Aspergillus: A. flavus, A. clavatus* and *A. parasiticus*), and cause aflatoxicosis (aspergillosis). The toxins are named as $B_1$, $B_2$, $G_1$ and $G_2$ (which fluoresce blue and green under long wave UV light). Order of toxicity: $B_1 > G_1 > B_2 > G_2$. Toxins are heat resistant and remain in feeds for years, even after the mould has died. All the species are susceptible. Afflicts severe economic losses to poultry and dairy farming.

**Toxicokinetics:** B1 in excess of 100 µg per kg of feed is toxic to cattle. Most of the ingested toxins bind to ruminal contents, but only 2-5 % reaches intestines from where they are absorbed. In blood the toxins bind to the plasma proteins. Slowly liver removes to toxins from blood and detoxicates them. The aflatoxins ($AFB_1$) are primarily metabolised by hepatic microsomal mixed function oxidases (cytochrome P-450 dependent) to epoxides, The $B_1$ is metabolized to $M_1$, $P_1$, $Q_1$ and $B_{2a}$ and aflatoxicol. $M_1$ is the most toxic (carcinogenic; excreted in milk). The aflatoxins and their metabolites are excreted in urine and bile (undergo entero-hepatic cycle).

**Mechanism of Toxicosis: Cytotoxicity:** Hepatotoxic, carcinogenic, teratogenic, mutagenic and immunosuppresants. All the effects result from binding of AFB1 and its metabolites to nuclear DNA and inhibition of synthesis of RNA, enzymes and other proteins.

Aflatoxins modify DNA template and interfere with function of DNA-dependent RNA ploymerase and mRNA synthesis. The toxins also bind to endoplasmic steroidal ribosome-binding sites causing disagrregation of ribosomes. Interference with both transcription and translation. Therefore, formation of enzymes or other essential .cellular macromolecules, clotting factors (prothrombin etc) is blocked leading to glycogen depletion, failure of energy metabolism. Cause disintegration of mitochondria and degeneration of hepatocytes. Immunosuppression (both humoral and CMI) predisposes to secondary infections.

**Clinical Signs and Necropsy**:

**Poultry**: Dejected appearance, reduced feed consumption, retarded growth, drop in egg production and generalized oedema, **PM**: Congestesd spleen and kidney, hepatic degeneration and enlarged bile duct.

**Cattle**: Blindness, circling, falling down, severe tenesmus, eversion of rectum, blood clotting defects and drop in milk yield. **PM**: Pale, fibrosed liver with centrilobular necrosis, enlarged bile duct, yellow kidney surrounded by wet fat, ascites and catarrhal enteritis.

**Pigs**: Inappetance, retarded growth and jaundice. **PM**: Off white to bright orange liver, enlarged bile duct and gross haemorrages in visceral organs.

**Dogs**: Anorexia, depression, polyurea, polydypsia and jaundice. **PM**: Haemorrages in thorax and peritoneum, yellow-mottled liver, necrosed gall bladder with haemorrhages, hepatic degeneration (fatty-necrosed: fibrosis).

In **general** the clinical signs are due to liver damage and blood clotting defects, which may be as under:

**Acute**: Anorexia, dullness, depression, nasal discharge, coughing, dyspnoea, anaemia, epistaxis, bloody feces, sometimes convulsions and sudden death.

**Subacute**: Janudice, hypoprothrombinemia, haematomas and haemorrhagic entertis.

**Chronic**: Gradual reduction in feed efficiency, productivity and growth rate; rough hair coat, anaemia, enlarged abdomen and jaundice.

**Lab. Investigations**:

1. Increase in serum transaminases (SGOT and SGPT), LDH and alkaline phosphatase (liver damage).
2. Elevated BUN (renal damage) and hyperbilirubinaemia (liver damage).
4. Suppressed cellular mediated and humoral immune responses.
5. Determination of aflatoxins in milk, meat and eggs (public health concern) and metabilites in urine.

**Treatment**:

1. Withdrawal of contaminated feed at once.
2. Low fat and high protein diet
3. Multivitamins, Se and Vitamin E.
4. Anabolic steroid stanozolol @ 2 mg/kg i/m at 4-5 day intervals.
5. Activated charcoal @ 6.5 mg/kg intrarumnally as 30% W/V slurry in phosphate buffer of pH 7.
6. Oxytetracycline @ 10 mg/kg i/m once a day.
7. I/V 5% dextrose
8. Hepatotonics.

**Prevention**: Hydrated sodium calcium aluminosilicate in feed at 0.5% (adsorbs the toxins and reduces their absorption from GIT – Toxin Binder).

**Ergotoxins**

These are toxins produced by the parasitic fungus belonging to *Claviceps* Genus: *C. purpurea, C. paspali* and *C. cinerea*, which grow on cereal crops and grasses under favourable conditions of humidity, moisture and temperature (rye, oats, barley, wheat, jowar etc and grasses *Paspalum scrobiculum, P. dilatatum* and *P. notatum*). Ergot infested jowar looks black (blackens on the plant itself before harvesting: Rejected as unfit for human use and so gets diverted for animal feeds). The disease thus occurs due to ingestion of ergot infested feeds is called Ergotism. Seen in all the animals, including poultry and even man (St. Anthony Fire).

The **toxic principles** of ergot are:
Alkaloids (derivatives of LSD): Ergot alkaloids: Ergotamine, ergometrine, ergocryptine, ergotoxine, ergostine etc). Other nitrogenous substances are: Acetyl choline, histamine and tyramine.

**Ergotism is of two types**: Acute and Chronic forms:
**Acute Form: (Nervous or convulsive ergotism)**: Rare, but results from ingestion of large quantity of ergot infested feeds by hungry animals.
**Mechanism of Toxicosis**: Ergot alkaloids (being the derivatives of LSD), histamine and tyramine interfere with the neurotransmission in CNS. The ergot alkaloids are 5-HT antagonists and also act as dopamine agonists in CNS. Therefore, the toxicity is characterized by nervous signs. They also depress the vasomotor and respiratory centres.
**Clinical Signs**: Hyperirritability, excitability, aggressiveness, muscular incoordination, spasms and tremors, ataxia, kicking, weakness, recumbency, hyperthermia (105 – 107$^{o}$F), respiratory depression and terminal convulsions. Death due to respiratory failure.
**Treatment**: Symptomatic. Remove the source at once and reduce the absorption from GIT (saline purgatives).

chronic form of ergotoxins are also called as Gangrenas

**Chronic Form: (Gangrenous ergotism)**: Common in farm animals.

**Mechanism of Toxicosis**: Ergot alkaloids cause intense constriction of smooth muscles of vasculature and stimulation of uterine muscles. Gangrenous ergotism results as follows: Vasoconstriction in the extremities – damage to capillary endothelium – thrombus formation – vasuclar stasis – loss of blood supply to the tips of the extremities [muzzle, limbs (hooves), ear and tail] – necrosis and gangrene of the affected parts – sloughing off of the affected parts.

**Clinical signs**: Diarrhoea, cold extremities, lameness, drop in milk yield and abortion.

**Treatment**: Remove the offending feed and switch over to new feed. Keep the animals in warm and clean quarters. Saline purgatives (remove the toxins from GIT), symptomatic treatment of affected areas. Broad spectrum antibiotics for treating necrotic lesions and secondary bacterial infections.

**Other Mycotoxins**

**Rubratoxins**: Produced by *Penicillium rubrum* and *P. purpurogenum*. Rubratoxins A and B are hepatotoxic (coexist with aflatoxins: synergistic hepatotoxic). Poisoning is common in monogastrics: Pigs most susceptible. Toxins are heat labile. Toxicosis like aflatoxins (binding to DNA, RNA etc).

**Ochratoxins**: Produced by *Aspergillus ochraceus and Penicillium viridicatum*. Nephrotoxic: Mold Nephrosis/Mycotic Nephropathy. Pigs are most sensitive. Kidney is the target organ: Proximal tubular epi. Cells: Polyurea, anuria – uremia. Also bind to plasma proteins, inhibit synthesis of tRNA and mRNA and increase free radical formation.

**Trichothecenes**: Produced by many molds (*Fusarium, Trichothecium, Myrothecium, Cephalosporium, Stachybotrys* spp. etc). The major trichothecenes are T-2 toxin, diacetoxyscirpenol and dioxynivalenol (vomitoxn). Inhibit, DNA, RNA and protein synthesis, transport of ions and metabolites across cell membranes and cause immune suppression, clotting defects (thrombocytopenia or inhibition of platelet aggregation) and GI irritation.

**Penitrem A**: Produced by *Penicillium cyclopium, P. palitans, P. viridicatum, P. crustosum*: Neurotoxic/Tremerogenic. Poisoning occurs in all spp. Ataxia, stiff gait and tonic convulsions

**Citreoviridin**: Produced by *Penicillium islandicum, P. citreoviridae*. Neurotoxic/Yellow Rice Toxin/ Moldy Polished Rice. (19th century in Japan: similar to thiamine deficiency (beri beri) thought to be due to B1 deficiency). Affects medulla: Neurotic signs, respiratory and vasomotor centres depressed.

**Zearalenone**: Produced by *Fusarium roseum, F. graminaerum*. Oestrogenic toxin: Pigs most sensitive: Hyperoestrogenic syndrome / Porcine Vulvovaginitis: Enlargement of vagina and vulva: 3-4 times to normal (Increased permeability to water) and increased vaginal secretions, prolonged oestrous cycle, enlarged mammary gland and uterus and atrophy of ovary. Not similar in structure to oestrogen, but acts through oestrogen receptors. Feminization in males: atrophy of testes.

**Slaframine**: Alkaloidal mold toxin produced by *Rhizoctonia leguminocola*, a mold that infests red clover. The toxin acts as histaminergic or through release of histamine. The animals which eat the mold-infested red clover hay develop a condition called **slobbers** with the signs of profuse thick salivation, urination, diarrhoea and lacrimation, fall in BP and dyspnoea.

**Fescue Toxins**: Produced by *Festuca aurindinacea*. Fescue Lameness/Fescue Foot: Lameness in one or both hind limbs, necrosis and gangrene of distal parts of limbs and extremities (ear and tips); Similar to ergotism: Cattle and Sheep.

**Lupinosis**: *Lupinus* spp. Lupine poisoning: nervous toxicity due to alkaloids in the plant (*L. digitatus, L. luteus, L. leucophyllus*) and Lupinosis (due to mold infestation by: *Phomopsis leptostromiformis*)

characterized by hepatotoxicity. In sheep and horses in US, Aust. and NZ. Spongy brain in sheep: Hyperexcitability, convulsions and central respiratory failure.

## 2. Bacterial Toxins

These are two types: Endotoxins and exotoxins. The endotoxin refers to lipopolyscahharide portion of cell wall of Gram negative bacteria. The endotoxins cause food-borne infection and are released when the bacteria are lysed or disintegrated. The endotoxins produce fever, vascular shock and generalized weakness. The endotoxins of *Salmonella* and *Shigella* cause gastroenteritis. The exotoxins are released into the media or surroundings (spoiled food) where the bacteria grow. Poisoning occurs following ingestion of contaminated foods. The exotoxins may be divided into three major groups basing on their effects:

a) Neurotoxins: Botulinum toxin and tetanus toxin (tetanospasmin)
b) Enterotoxins: Cholaragen
c) Histotoxins (Cytotoxins): Diphtheria toxin and hemolysins.

**Botulinum Toxin**: A neurotoxin produced by *Clostridium botulinum*; causes botulism. It acts by binding to presynaptic motor nerve terminals, preventing the presynaptic release of ACh (probably through interfering with role of $Ca^{++}$ ions in the cholinergic neurons), interfering with impulse transmission at neuromuscular junction (MEP) and causing flaccid paralysis of skeletal muscles (respiratory muscles including the diaphragm). Botulinum toxin is very highly toxic ($LD_{50}$ in lab animals: 10 ng/kg). Treatment consists of injection of botulinum antitoxin (polyvalent or specific), artificial respiration and other supportive measures.

**Tetanospasmin**: A neurotoxin produced by *Clostridium tetani*; causes tetanus. The bacteria release the toxin in animal body upon autolysis. It has selective action on spinal neurons. The toxin migrates through motor nerves into the spinal cord, where it interferes with the function of inhibitory transmitter glycine in spinal synapses. The toxin, being a protease breaks the synaptic vesicular membrane protein synaptobrevin and prevents release of glycine from spinal nerve terminals. Therefore tetanospasmin causes unchecked excitation of spinal neurons leading to potent spasmodic tonic contractions of skeletal muscles. Horse and man are the most susceptible species. The affected horse may assume the posture resembling sea horse stance (spasm and stiffness of neck, back and leg muscles). Death is due to respiratory failure (tonic paralysis of larynx, diaphragm and intercostals muscles). Treatment consists of injection of tetanus antitoxin and penicillin; symptomatic treatment to control tonic spasms (chlorpromazine + phenobarbitone). Passive immunity can also ensured by injections of tetanus antitoxin.

**Cholaragen**: It is the cholera toxin (enterotoxin) produced by *Vibrio cholerae*. The toxin increases cAMP formation by stimulating adenyl cyclase; causing enhanced secretion of chlorine and bicarbonate ions from mucosal cells into the intestinal lumen, altered osmotic balance, withdrawal of large volumes of water into the lumen and finally resulting in severe watery diarrhoea. An enterotoxin of *E. coli* also acts in similar fashion.

**Diphtheria toxin**: It is a cyototoxin (histotoxin) produced by *Cornybacterium diphtheriae*; exerts cytotoxicity through inhibition of protein synthesis in mammalian cells, by blocking transferase reaction during translation of mRNA and preventing addition of amino acids in elongation of peptide chain. An enterotoxin of *Pseudomonas aeuriginosa* also exerts similar cytotoxic action.

**Hemolysins**: The cytotoxic toxins streptolysin O and streptolysin S are produced by *Streptococcus* spp. cause lysis of human RBCs. *Staphylocossus aureus* and *Clostridium perfringes* also produce cytotoxins leucocidin and lecithinase (alpha toxin) respectively. Leucocidin selectively causes lysis of leucocytes. Lecithinase causes lysis of RBC as well as other tissue cells.

## 3. Zootoxins

The extremely poisonous compounds/toxins elaborated by the lower animals are called zootoxins.

**Snake Venoms:**

Venomous snakes are two types:

1. **Elapines**: These include cobra, krait, mamba and coral snakes. These have short fangs, hang on and chew venom into their victims. Venom is **neurotoxic** and cause death due to paralysis of respiratory centre and muscles (Curariform effect).
2. **Vipers**: These include Russel's viper, pit viper, rattle snake and puff adder. These have long, hinged, hollow fangs, they strike and inject venom and immediately withdraw. Venom is mainly haemotoxic, necrotizing and anti-coagulant and/or coagulant, but also has a neurotoxic component.

**Composition of snake venoms:**

**Proteins:**

a. **Enzymes**: Proteases, hyaluronidase, collagenase, lipases, AChE, ribonuclease, deoxyribonuclease, phospholipases, amino acid oxidases and thrombin like coagulative enzyme.
b. **Non-enzymatic**: Low mol. wt. polypeptides (neurotoxins, haemotoxins, cytotoxins, toxalbumins etc).

Cobra venom has two neurotoxins: **α–bungarotoxin** (blocks postsynaptic cholinergic nictonic receptos) and **β–bungarotoxin** (like botulinim toxin prevents release of ACh from presynaptic nerve terminals). The actions of the two toxins at the neuromuscular junction results in paralysis of skeletal muscles including the respiratory muscles.

**Others**: Lipids, steroids, glycoproteins, amines and minerals and metals (Na,Ca,K, Mg, Zn, Co, Fe etc).

Fatal snake bites are common in dogs (attack snakes and small body size). Cats avoid snakes. Horses and cattle seldom die (except when bitten on head (muzzle/lips) or neck) due to large size. Pigs are less susceptible (poor absorption due to layer of s/c fat).

**Clinical Signs:**

Restlessness, excitement, calmness and depression, followed by incoordination, collapse and death.

**Viper bite** is chatacterized by local tissue damage, which spreads from bite site, discolouration of tissues, oozing of dark bloody fluid from fang wounds,swelling, local suppuration, sloughing and gangrene, tetanus and death due to septicaemia. Death within 2-4 days.

In **elapine bites**, pain and swelling are minimal, but systemic neurological signs dominate. Excitement, muscle weakness, incoordination, paralysis, difficulty in swallowing, viscid salivation and marked pupil dilatation. Convulsions precede death due to krait bite. Death within 20 min to 6 hr.

**Diagnosis**: History, circumstantial evidence, recognition of fang marks and clinical signs.

**Lab. Investigations**: Elevated plasma creatine kinase released from degenerated muscles, prolonged clotting time, haemoglobinuria or myoglobinuria.

**Treatment and Management:**

**Specific Therapy**: Should be initiated at soonest possible time.

**Antivenin**: Polyvalent Antisnake Venom: Dog: Up to 100 ml, 5–10 ml into tissues around bite site and rest iv; Large Animals: 20 ml (2 units)/150 kg iv.

To counter anaphylactic reactions Adrenaline (1:1000) @ 0.5-1 ml sc

**Supportive Therapy:**

a. Limb movements/exercise promote absorption, therefore the animal should be kept under complete rest.
b. Application of a pressure bandage/tourniquet above the bite site, to be loosened at 10 min intervals (in elapine snake bite, but contraindicated in viperine bite: local tissue necrosis.
c. Fluid therapy (lactated Ringer's solution)
d. Corticosteroids prolong the clinical course (Buying Time).

e. Tetanus antitoxin.
f. Anti-histamines are advised (diphenhydramine).
g. Blood transfusion (haemolytic or anticoagulant venoms).
h. Broad spectrum antibiotics to prevent wound infection (*Pseudomonas, Clostridial, Cornybacterium* and *Staphylococcus* Spp. are isolated from snakes' mouth.).

**Differentiation between Poisonous and Nonpoisonous Snakes:**

**1. Belly Upwards:**

a. If the belly scales are small like those on the back, the snake is not poisonous.
b. Moderately large belly scales that do not cover the entire breadth suggest that snake is not poisonous.
c. Large belly scales that cover the entire breadth suggest that the snake may be poisonous or nonpoisonous.

**2. Top of the Head:**

a. Small scales on the head suggest that the snake is poisonous and one of the vipers.
b. Large scales on the head suggest that snake may be nonpoisonous or poisonous.

**Identification of Vipers and Cobra:**

a. If there is a conspicuous opening or 'pit' between the eye and the nostril, the snake is poisonous and one of the pit vipers.

If the third labial touches the eye and the nasal shields, the snake is poisonous, being a cobra or a coral snake.

### 3. Other Zootoxins

| Species | Venom/Toxin | Mode of action | Clinical Signs | Treatment |
|---|---|---|---|---|
| Scorpion | Neurotoxic venom, histamine, hexosamine, 5-HT, kinins, enzymes (AChE, hyaluronidase, phospholipases) | Persistent depolarization (increase $Na^+$ permiability of nerves): over stimulation and paralysis | Pain and swelling at site of sting. nervous signs muscular tremors, convulsions | Local: Tourniquet, injection of analgesics at site, sedatives. Anti-scorpion serum (i/v) |
| **Spiders:** American black widow spider (*Latrodectus mactans*) Brown widow spider Red legged/ Jumping/ Running spiders | Neurotoxin: Alpha Latrotoxin Histamine, 5-HT, intestinal spasmogenic polypeptides and enzymes: hyaluronidase, proteolytic enzymes and esterases | Latrotoxin releases excess Ach: persistent depolarization of motor nerves: initial stimulation and then paralysis of muscles | Man, dog and cat Pain and swelling at site. Abdominal muscle spasms, emesis, nervous excitement, dyspnoea, paralysis. Death within 4 to 6 hr. | Symptomatic. Antihistamines, i/v fluids: calcium borogluconate, respiratory stimulants. |

| | Venom / Toxin | Mode of Action | Clinical Sign | Treatments |
|---|---|---|---|---|
| **Toads:**<br>*Bufo vulgaris*<br>*B. regularis*<br>*B. alvarious (rivers)*<br>*B. marinus (sea)* | Cardiotoxic glycosides: bufogenin and bufotalin and Neurotoxic: bufotoxin (formed in skin and stored in parotid glands). Skin secretions also contain histamine, tyramine, epinephrine and Norepinephine | Selective increase in Na ion permeab.: persistent depolarization of nerves | Ingestion in dog & cat.<br>Salivation, emesis, cardiac arrhytmia, resp.distress, convulsions, collapse and death within 2 to 6 days. | Wash mouth with lots of water. Activated charcoal, saline purgatives, atropine, antihistamines datives/ tranquilizers. Propranolol (0.2 mg/kg iv) to check atrial fibrillation |
| **South American Frog** | Batrachotoxin: A steroidal alkaloid | Batrachotoxin causes selective increase in Na ion permeability, persistent depolarization of nerves | | |
| **Fishes:**<br>Puffer fish<br>Shell fish | **Ichthyotoxins:**<br>Tetrodotoxin<br>Saxitoxin | Selective blockade of $Na^+$ permeability and nerve paralysis. | Paralysis. Respiratory and cardiac failure | Symptomatic |
| Moray eel | Ciguatoxin | Selective increase in $Na^+$ perm, persistant depolarization of nerves | Nervous signs followed by paralysis | Symptomatic |
| **Bees and Wasps:**<br>Honey bees etc. | Melittin (antigenic protein), histamine, kinins, 5-HT, hyaluronidase and phospholipases | Allergic reactions (man/horses) | Pain, burning sensation and swelling at site. Excitement, tachycardia, dyspnoea, jaundice and haemoglobinuria | Application of weak ammonia or soda bicarb solution on the site. Antihistamines, sedatives and cortisone. |
| **Ticks:**<br>*Dermacentor andersoni*<br>*D.occidentalis*<br>*Hemophysalis punctata*<br>*Hyalomma aegypticum*<br>*Ixodes holocyclus, I.pilosus,*<br>*Rhiphicephalus evertsi* | A variety of toxins secreted by the salivary glands of female ticks : | Anticholinergic: Blockade of ACh synthesis and/or release from motor nerve terminals. Paralysis of skeletal muscles and respiratory failure. | Tick paralysis (lambs, kids, calves and dogs): muscle weak-ness, incoordination, mydriasis. | Symptomatic. Removal of ticks from body surfaces. Tick control measures: Insecticide/ acaricide sprays. |

## EXERCISE

1. What are toxins? Give the classification of bacterial toxins and describe in brief the mechanisms of their intoxication.
2. What are toxins? Give the classification of mycotoxins. Describe ergotism.
3. What are mycotoxins? Give their classification with sources. Describe aflatoxicosis in poultry.
4. What is ergot? What are its toxins? Describe chronic ergotism in animals.
5. What are zootoxins? Give their classification. Describe snake venoms giving a brief account of their nature and clinical signs, diagnosis and treatment of snake bite victims.
6. What are aflatoxins? Discuss in brief the mechanism of toxicosis, toxicokinetics, clinical signs, diagnosis and treatment and prevention of aflatoxicosis in poultry.
7. **Write a short note on the following:**
   a) Botulinum toxin
   b) Tetanus toxin
   c) Gangrenous ergotism
   d) Nervous ergotism
   e) Rubratoxins
   f) Zearalenone
   g) Ochratoxins
   h) Trichothecenes
   i) Neurotoxic venom
   j) Haemotoxic venom
   k) Bee stings
   l) Scorpion toxins
   m) Toad toxins
   n) Ichthyotoxins
   o) Tick paralysis
   p) Snake venoms
   q) Composition of snake venoms
8. **Differentiate between the following:**
   a) Toxin and zootoxin
   b) Phytotoxin and zootoxin
   c) Hemotoxic venom and neurotoxic venom
   d) Acute ergotism and chronic ergotism
   e) Viperine bite and elapine bite
   f) Viperine bite and cobra/krait bite
   g) Bufotoxins and icthyiotoxins
   h) Latrotoxin and bufotoxin
   i) Tetradotoxin and ciguatoxin
   j) Tetanus toxin and botulinum toxin
   k) α-Bungarotoxin and β-bungarotoxin
   l) Endotoxin and exotoxin
   m) Neurotoxin and enterotoxin
   n) Zearalenone and slaframine
9. **Describe mechanism of toxicity of the following:**
   a) Aflatoxins
   b) Ergotoxins
   c) Tick toxins
   d) α-Bungarotoxin
   e) β-Bungarotoxin
   f) Slaframine
   g) Zearalenone
   h) Rubratoxins
   i) Ochratoxins
   j) Trichothecenes
   k) Tetradotoxin
   l) Saxitoxin
   m) Ciguatoxin
   n) Melittin
   o) Tick toxins
   p) Scorpion venom
   q) Latrotoxin
   r) Spider venom
   s) Bufotoxins
   t) Batrachotoxin
10. **Give the line of treatment of the following:**
    a) Snake bite in a dog/goat
    b) Bee stings in dog/horse
    c) Tick paralysis in a lamb
    d) Tetanus in dog/horse
    e) Botulism in a dog
    f) Aflatoxicosis in poultry
    g) Chronic ergotism in cattle
11. **What do you mean by the following? Answer in one or two sentences for each:**
    a) Ergotism
    b) Aflatoxicosis
    c) Aspergillosis
    d) Latrotoxin
    e) Melittin
    f) Ichthyotoxins
    g) Bungarotoxins
    h) Tick paralysis
    i) Tetanus toxin
    j) Botulinum toxin
    k) Spider venoms
    l) Elapines
    m) Vipers
    n) Elapine venom
    o) Viper venom
    p) Exotoxin
    q) Endotoxin
    r) Rubratoxins
    s) Ochratoxin
    t) Trichothecenes
    u) Oestrogenic toxin
    v) Histaminergic toxin
    w) Aflatoxins
    x) $M_1$ toxin
    y) Cytotoxin
    z) Enterotoxin
    aa) Slobbers
    bb) Lupinosis
    cc) Fescue foot
12. **Matching** (parallel pairs):
    a) Aflatoxin $B_1$: Hepatoxic
    b) Aflatoxin $M_1$: Carcinogenic
    c) Ergotoxins: *Claviceps purpurea*
    d) Aflatoxins: *Aspergillus flavus*
    e) Zearalenone: *Fusarium roseum*
    f) Rubratoxins: Hepatoxic
    g) Ochratoxins: Nephrotoxic
    o) Tetanus: Convulsion
    h) Trichothecenes: Neurotoxic
    i) Zearalenone: Oestrogenic
    j) Slaframine: Histaminergic
    k) Ergotoxins: Lameness
    l) Fescue toxins: Lameness
    m) Elapine venom: Neurotoxic
    n) Viper venom: Hemotoxic

p) Tetradotoxin: Puffer fish
q) Saxitoxin: Shell fish
r) Ciguatoxin: Moray eel
s) Melittin: Bee sting
t) Bufotoxin: Neurotoxic
u) Tick toxins: Anticholinergic
v) Melittin: Allergic reactions
w) Cholaragen: Enterotoxin
x) Leucocidin: Lysis of WBCs
y) Leucocidin: *Staph. Aureus*
z) Lecithinase: *Cl. Perfringens*
aa) Lecithinase: Alpha toxin
bb) Lecithinase: Lysis of RBCs
cc) Streptolysins: Hemolysins
dd) Lecithinase: Lysis of RBCs
ee) King cobra: Naja henna
ff) Indian krait: Bangarus niger
gg) Black krait: Bangarus calrulens
hh) Saxitoxin: Ichthyotoxin
ii) Tetradotoxin: Ichthyotoxin
jj) Ciguatoxin: Ichthyotoxin
kk) Botulinum toxin: Flaccid paralysis
ll) Tetanospasmin: Tonic paralysis
mm) Sea horse stance: Tetanus
nn) Diphtheria toxin: Cytotoxin/Histotoxin
oo) Tetradotoxin: Blockade of $Na^+$ permeability
pp) Saxitoxin: Blockade of $Na^+$ permeability
qq) α-Bungarotoxin: Nicotinic receptor blocker
rr) β-Bugarotoxin: Blocks Ach releases
ss) Ciguatoxin: Persistent depolarization
tt) *Dermacentor andersoni*: Tick toxins
uu) Tetradotoxin/Saxitoxin/Ciguatoxin: Ichthyotoxin
vv) Scorpion venom: Persistent depolarization
ww) α-Latrotoxin: Excess Ach release/persistent depolarization
xx) Bufogenin/bufotalin: Persistent depolarization
yy) Bufogenin/bufotalin: Increase in $Na^+$ permeability
zz) Batrochotoxin: Increase in $Na^+$ permeability
aaa) Batrachotoxin: Persistent depolarization
bbb) Batrachotoxin: Steroidal alkaloid toxin
ccc) Citreoviridin: Yellow rice toxin/moldy polished rice
ddd) Zearalenone: Porcine vulvo-vaginitis/ hypertrophy or enlargement of vulva and vagina

13. **Substantiate each of the following statements by giving the most appropriate reason in one or two sentences**:
    a) Aflatoxins are teratogenic, mutagenic, immunotoxic and carcinogenic.
    b) Aflatoxins are hepatotoxic.
    c) Aflatoxin M1 is considered toxic.
    d) Aflatoxin metabolites are also toxic.
    e) Aflatoxicosis results in delayed blood clotting.
    f) Aflatoxicosis is characterized by hepatotoxicity.
    g) Aflatoxins are immunosuppressive.
    h) Aflatoxicosis in dairy animals is of public health concern.
    i) Hydrated sodium calcium aluminosilicate (HSCAS) can help in preventing aflatoxicosis.
    j) Aflatoxicosis is characterized by elevated serum GOT/GPT, LDH and alkaline phosphatase.
    k) HSCAS helps in preventing absorption of dietary aflatoxins.
    l) Acute ergotism is characterized by nervous signs.
    m) Chronic ergotism is characterized by lameness.
    n) Chronic ergotism is called gangrenous ergotism.
    o) Sloughing off of tips of extremities occurs in chronic ergotism.
    p) Ergotoxins interfere with blood supply in the extremities.
    q) Rubratoxins interfere with protein synthesis.
    r) Zearalenone is an oestrogenic toxin.
    s) Slaframine causes fall in BP and dyspnoea.
    t) Zearalenone results in feminization in males.
    u) β-Bungarotoxin causes respiratory failure.
    v) α-Bungarotoxin causes respiratory failure.
    w) Bungarotoxins cause curariform effect.
    x) Cobra bite results in death due to respiratory failure.
    y) Neostigmine/Edrophonium has synergistic action with antisnake venom.
    z) Scorpion bite causes intense pain.
    aa) Spider toxin causes initial stimulation followed by paralysis of skeletal muscles.
    bb) Bufogenin/Bufotalin causes cardiac arrest.
    cc) Bufotoxin causes neurotoxicity.
    dd) Venom of South American frog causes neurotoxicity.
    ee) Puffer fish/Shellfish toxin causes paralysis of nerves.
    ff) Tetradotoxin/Saxitoxn causes nerve paralysis.

gg) Ciguatoxin/Moray eel toxin causes nervous signs.
hh) Tick toxins cause paralysis of skeletal and respiratory muscles.
ii) Tick infestation with *Ixodes, Hyaloma* or *Dermacentor* spp. may cause tick paralysis.
jj) Botulinum toxin causes muscle paralysis.
kk) Tetanus toxin causes violent convulsions
ll) Streptococcal toxins are called hemolysins.
mm) Diphtheria toxin is a histotoxin/cytotoxin.
nn) Cholaragen/enterotoxin causes diarrhoea.
oo) Generalized muscle paralysis occurs following a cobra/krait bite.
pp) Application of tourniquet prolongs the life of a snake bite victim.
qq) Aflatoxicosis predisposes to secondary infections.

# Chapter – 49: ENVIRONMENTAL TOXICOLOGY

## 1. Food Toxicants

**Plant origin**: Cyanogenic glycosides, selenium, nitrates/nitrites, oxalates, ricins etc.
**Microbial origin**: Toxins elaborated by pathogenic microorganisms (fungi and bacteria)
**Endotoxins**: Food borne disease (food infection): Specific incubation period/responds to antibiotics.
**Exotoxins**: Mycotic and bacterial toxins: Food poisoning/intoxication: No incubation period; immediate effects. Need specific treatment or antitoxins.
**Environmental Pollutants**: Feed Contaminants (Chemical and biological pollutants: Heavy metals, chemicals, drugs, agrochemicals, industrial effluents and domestic/urban wastes.

**2. Feed Additives**: These are intentionally added to the animal feeds with a purpose and include: Anabolics, Antibiotics (disease prevention), Ionophores, Nutrient supplements (urea/vitamins) and the others as below:
**Anticaking/Antilumping**: Calcium silicate or Aluminium-calcium silicate
**Antioxidants**: Ascorbic acid or triethyl citrate
**Coloring agents**: Amaranth (red), Tartrazine (yellow/orange) or scarlet red
**Emulsifying agents**: Cholic acid, gum tragacanth
**Flavouring agents**: Safrole, maltol, methyl anthranilate
**Artificial sweetners**: Saccharin/sodium cyclamate
**Preservatives**: Benzoic/sorbic/salicylic acids
**Stabilizers**: Acacia, agar-agar
**Drying agents**: Bisulfites (Sodium meta-bisulfite)
**Humectants**: Glycerine
**Antinutrients**: Tannins, lectins, phytates, trypsin inhibitors etc.

## 3. Indices of Levels of Toxicants in Feeds

**Residue** it is the quantity of a drug, any chemical contaminant or toxicant or its metabolite that is present in the food or feeds at the time of ingestion and may be a cause of health hazard to the consumer (man)

**Withdrawal Period** is the period of gap from the time of last exposure to the time intended for harvesting, slaughter or consumption.

**Aceptable Daily Intake (ADI)** is defined as the quantity of a chemical that would not cause appreciable risk to the health of a person when it is consumed daily during the entire life span on the basis of all the facts known at that time of evaluation of the chemical. The ADI is expressed as mg per kg body weight per day.

**Maximum Residue Level (MRL)** is the maximum concentration of a pesticide residue recommended by the Codex Alimentarius Commission to be legally permitted in or on food commodities and animal feeds. It is expressed as mg/kg. The MRLs in milk or milk products and meat or meat products are expressed on per cent basis in fat.

**Extraneous Maximum Residue Limit (EMRL)** is the maximum concentration of a pesticide residue or contaminant that is recommended by the Codex Alimentarius Commission to be legally permitted or recognized as acceptable in or on a food, agricultural commodity or animal feed. It is expressed as mg of pesticidal residue (or contaminant) per kg of the food or feed. The EMRL refers to the residue of a pesticide or contaminant arising from environmental sources (including prior agricultural use) other than the use of a pesticide or contaminant directly or indirectly on the commodity.

**Acute Recommended Reference Dose (RfD)** is defined as an estimate of the amount of a substance in food and/or drinking water, normally expressed on body weight basis, that can be ingested in a period of 24 hr or less without appreciable health risk to the consumer on the basis of all known facts at the time of the evaluation. It is a short-term dietary intake assessment of pesticide residue intake over a single day.

**No Observable Effect Level (NOEL), No observable Aderse Effect Level (NOAEL) or Maximum No Adverse Effect level (MNAEL)** is defined as the largest dose of a drug or chemical when administered over a given period of time, which does not cause any observable adeverse effect in the animal. It is also expressed as mg per kg body weight per day. NOAEL is more than the ADI

**Lowest Observable Effect Level (LOEL, LOAEL)** is defined as the lowest dose of a drug or chemical when administered over a given period of time produces an observable effect related to the drug or chemical.

**Tolerance Level (Tolerances)** is defined as the maximum concentration of a residue of a drug or chemical in food materials that can be permitted at a specific period of harvesting, slaughter or processing; storage or marketing up to the time of ingestion by the consumer. It is expressed as ppm (parts per million: mg/kg or mg/L; ppb (parts per billion: µg/kg or µg/L) or ppt (parts per trillon: ng/kg or ng/L). Tolerances can be:

**Finite Tolerance**: Measuarable amount of resudue of a noncarcinogenic drug/chemical in food materials.
**Negligible Tolerance**: Insignificant or negligible amount of residue of a drug/chemical in food materials.
**Zero Tolerance**: Nil amount of a carcinogenic or extremely toxic substance in food materials.

## 4. Common Toxicants in Animal Feeds

| Toxicant/Source | Toxicological Considerations | Treatment/Prevention |
|---|---|---|
| Gossypol: Polyphenolic compound. Cotton seed cake (CSC) | CSC with gossypol up to 0.01% (100 ppm) is safe and > 300 ppm is toxic. More toxic in monogastrics (pig and poultry). Cumulative (1-3 months feeding). Anorexia, weakness, cough, dyspnoea, gastroenteritis/diarrhoea, luteolysis in females, sterility in males (sperm abnormalies and suppression of testosterone synthesis) and hematuria. Death due to myocardial degeneration and heart failure. | Change the feed. Detoxify cake by adding calcium carbonate at 1% or ferrous sulfate at 0.1%. |
| Mimosine, nonprotein amino acid in *Mimosa pudica* (sensitive plant) and *Leucaena leucocephala* (Subabul), a leguminous green fodder source | Lone feeding is toxic. Mimosine yields a goitrogen 3,4-dihydroxypridone (DHP), on mastication it is converted to 2,3-DHP; all 3 are goitrogenic (inhibit thyroxine synthesis). Mimosine daily intake > 0.15-0.20 gm/kg body weight is toxic in ruminants. Alopecia (destructon of hair follicles), feeding in pregnant animals results hypothyroidism in new-borns, anoestrum, failure of conception, lameness and mouth ulcers, hair loss of mane and tail in horse, fetal resorption etc. *Leucaena* toxicity is also called jumbey or lamtoro. | Withdrawal of feeding reverses toxicity;, steaming of leaves or adding ferrous sulfate @ 1% in feed reduces toxicity. Sole feeding to be avoided. |
| Linamarin: Cyanogenic glycoside. | Oil extracted linseed cake of immature seeds. Oil extraction destroys the cyanogenic glycosidase. | As in cyanogenic plant poisoning |
| Phytates: Til cake (*Sesamum indica*) | Phytates interfere with calcium absorption from GIT | Change the feed. Ca feed supplements. |

| | | |
|---|---|---|
| Sinigrin:Glycoside in mustard seed cake (*Sinipis alba/nigra*) Rape seed cake (RSC, *Brassica napus*) | Sinigrin causes retarded growth rate, acute gastroenteritis, colic and diarrhoea. Its breakdown products allyl cyanide and allyl isothiocyanate cause hemolysis. RSC and cabbage (*Brassica* spp) also have a progoitrin (glucosinolate) which yields thiocyanate (goitrogenic), pulmonary emphysema/oedema, loss of appetite, ruminal atony, constipation and haemoglobinuria. | Change the feed. Symptomatic treatment. |
| S-methyl-L-cysteine sulfoxide (SMCS) in *Brassica* spp(Rape, cabbage, cauliflower); *Allium* spp (Onion) | Ruminal microflora converts SMCS to dimethyl sulfide which causes hemolytic anaemia and pulmonary emphysema. | Withdraw feeding. Symptomatic. Hematinics. |
| Solanine *Solanum tuberosum* (Potato) | Common in pigs. Green, unripe, old or rotten potatoes and sprouting tubers are rich in solanine (glycoalkaloid). Potatoes upon exposure to sunlight turn green. Solanine has irritant action on GIT mucosa, after absorption lysis of RBC, CNS stimulation followed by depression (respiratory and vasomotor centres). Death due to cardiac arrest | Saline purgatives. Respiratory & cardiac stimulants. Steaming or cooking of potatoes destroys solanine. |
| Ionophores: Monensin Lasalocid Salinomycin Narasin (*Streptomyces* spp.) | Coccidiostats in poultry (@ 100 gm/ton of feed). To improve feed efficiency in cattle @ 5-30 ppm in finished ration. Alter rumen function and increase propionic acid production). Interfere with K transport into mitochondria, inhibit ATP hydrolysis and reduce cellular energy production. Ionophores promote free radical formation, excessive lipid peroxidation, impaired oxidative phsophorylation, death of myocytes (excess $K^+$ efflux and $Ca^{++}$ influx). Horses are most susceptible, followed by dogs and cattle, and poultry least susceptible. Clinical signs: Depression, weakness, ataxia, dyspnoea and diarrhoea. | Change the feed, giving activated charcoal and supportive therapy. |

## 5. Feed Additive Toxicity

**Oestrogen Feed Supplementation:** It is done for promotion of growth and development, especially in feed-lot cattle and poultry. The other souces of oestrogen toxicity in animals include phytooestrogens (oestrogenic plants), oestrogenic mycotoxin toxin zearalenone, pasture contamination by dung of oestrogen supplemented feed-lot cattle and feeding of dried litter from poultry houses where oestrogen supplementation was done. The clinical signs of oestrogen toxicity include oestrogenism and retardation of testicular development in males; urethral obstruction (narrow lumen and caliculi), prolapse of vagina, rectum and uterus in lambs; prolapse of rectum and incontinence of urine in pigs and nymphomania and prolapse of rectum and vagina in cows.

**Dried Poultry Litter**: It is used as a feed supplement as source of nitrogen in ruminants. Feeding poultry waste may cause toxicity of copper and oestrogen (supplementation in poultry feeds). The toxicity signs include hypoalbuminemia, ascites (in lambs), renal impairment, anaemia, hepatic degeneration (even necrosis) etc and botulism may also occur.

**Brewer's Residues**: Feeding of beer residues may get contaminated with *Aspergillus flavus* and cause aflatoxicosis in animals.

**Chocolate Poisoning:** Chocolate is obtained from roasted seeds of *Theobroma cocoa*. The toxicity is due to methylxanthines theobromine and caffeine (antagonism of adenosine in CNS). Its toxicity characterized by cardiac arrhythmia, increased thirst, vomiting, diarrhoea, CNS excitation and tremors or convulsions and occurs in dogs (excess feeding of chocolates to pet dogs). Treatment is symptomatic (diazepam and propranolol).

**Chemical-Treated Grains**: Formalin-treated grains are fed to dairy cows to promte polyunsaturated fat content in milk products (formalin prevents hydrogenation of grain fat in rumen). Improper mixing or high formalin content in grains causes toxicity (rumenitis and diarrhea). Feeding of caustic-treated grains (to improve digestibility) may result in renal damage and abomasal ulceration in ruminants.

## 6. Environmental Pollution

**Environment**: Surroundings i.e. air, water and earth of living organisms

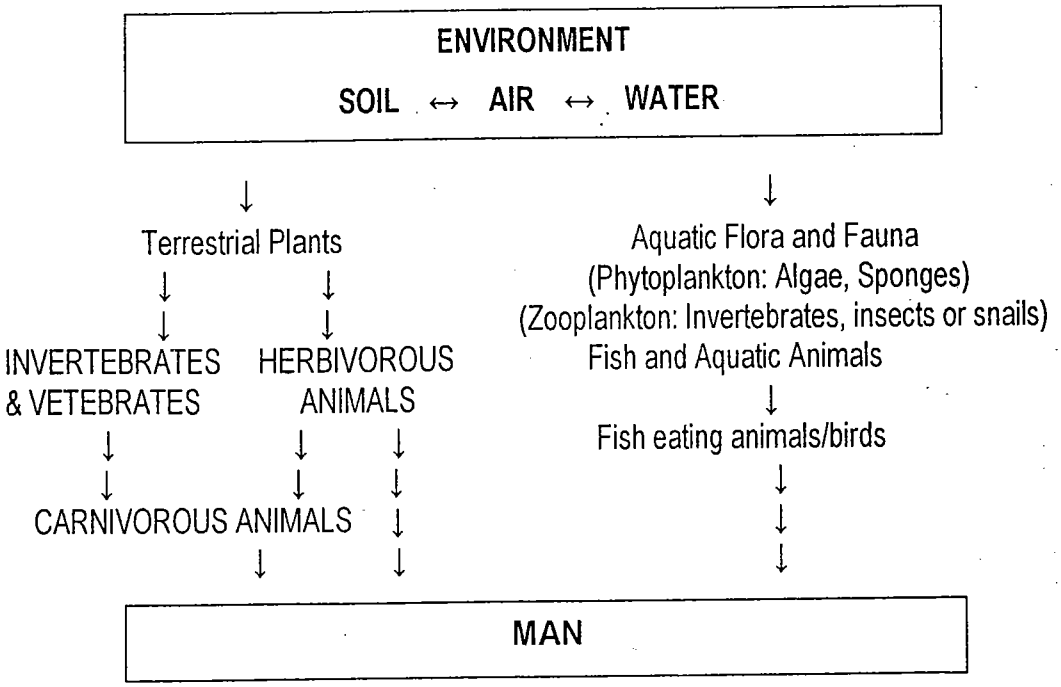
**Pollution**: Addition of harmful or unpleasant substances.

**Environmental Pollution**: Deterioration in the quality of environment (air, water and soil) due to contamination with harmful agents: Chemical, biological or physical. Threatens healthy survival of living organisms.

**Environmental Toxicology**: Branch of toxicology which deals with the study of environmental pollutants and their harmful effects on the ecosystem.

**Biological Magnification**: Increase in concentration of a chemical in upward direction of food chain (DDT: Decrease in number of vultures/wild birds/crows etc)

**Biological Transfer of Chemical Pollutants: FOOD CHAIN**




**Air Pollution**

**Sources**:

1. Fossil Fuel Combustion: Thermal power plants, industrial furnaces and domestic fires)
2. Automobile exhausts
3. Industrial emissions

**Major Air Pollutants**: CO: 52%; Sulfur Oxides: 18 %; Hydrocarbons: 12 %; Particulate matter: 10 % and Nitrogen Oxides: 6 %

**Carbon Monoxide**: Toxicity is due to formation of Carboxy Hb (220 > affinity than $O_2$). No oxygen supply to tissues: Hypoxia or Anoxia.
**Clinical Signs**: Laboured breathing and increase in heart rate, vasodilatation, enhanced anaerobic glycolysis and lactic acidosis

**Sulfur Dioxide**: Irritant to eyes and lungs.
Causes acid rain: $SO_2 + 2H_2O \rightarrow \mathbf{H_2SO_4} + H_2$ (Acid comes to earth as acid rain)
**Clinical Signs**: Bronchial irritation/constriction: Asphyxia. Conjunctivitis

**Hydrocarbons**:
Gases: Methane, ethane, propane and butane: Bronchial irritation/constriction: Asphyxia
Solvents: n-hexane, methanol, benzene etc: CNS depression; Dizziness. Incoordination
Petrol/Kerosene: Ingestion: Excitement, incoordination, ataxia, delirium and coma
Vapors: Sensitize myocardium to circulating epinephrine, precipitate ventricular fibrillation and cause central respiratory failure.
Gasoline (petrol) has 2 % benzene.

**Methanol**: Industrial solvent, paints/varnishes. Ingestion of 15 ml causes blindness and 70-100 ml causes death.

$$\text{Methanol} \xrightarrow{\text{Alcohol Dehydrogenase}} \text{Formaldehyde} \xrightarrow{\text{Alcohol Dehydrogease}} \textbf{Formic acid (blindness)}$$

**Clinical Signs**: Visual disturbances: irreversible blindness and central respiration failure.
**Treatment**: Ethanol: Competitive antagonist of alcohol dehydrogenase. Administration of 4-methyl pyrazol (specific inhibitor of alcohol dehydrogenase.
**Benzene**: Automobile emissions (main source): Carcinogenic. Inhalation: CNS depression, nausea, vomiting, staggering, blurred vision, tremors, ventricular fibrillation, respiration failure. Chronic exposure leads to aplastic anaemia (bone marrow depression) and leukemia.

**Nitrogen oxides**: Nitrogen dioxide: Lung irritant: Causes pulmonary oedema. $NO_2$ liberated from silage causes **Silofillers Disease**.

**Recycling of nitrogen dioxide and Ozone in atmosphere**

$$NO_2 \xrightarrow{\text{UV radiation}} NO + O; \quad O + O_2 \rightarrow O_3 \text{ (ozone)}; \quad NO + O_3 \rightarrow NO_2 + O_2$$

Photochemical smog: Refers to gery or brown air/haze in urban areas (metros) due to pollution of hydrocarbons (HC) and nitrogen oxides (mainly from automobile exhausts).

$$HC + NO + O_2 \rightarrow NO_2 + \text{PAN (peroxyacetyl nitrate)}$$

PAN damages chloroplasts causing decrease in photosynthetic efficiency of plants and thus retards their growth. Nitrogen oxides contribute to acid rain through formation of $HNO_3$. Acid rains ($H_2SO_4$ and $HNO_3$) lower the pH of surface water, leach Ca, Mg, K and Na out of the soil into groundwater resulting in soil infertility. Excessive salts into soil also results in salinity causing reduced plant growth and also affect health and productivity of livestock.

In atmosphere UV radiation accelerates ozone ($O_3$) formation ($NO_2 \rightarrow NO + O$; $O + O_2 \rightarrow O_3$). Ozone is an irritant to lungs and eyes and causes bronchoconstriction, pulmonary oedema, conjunctivitis or blindness.

In stratosphere short wave UV light converts $O_2$ to $O_3$ (ozone layer: Absorbs UV radiation and protects earth). Depletion of ozone layer: Intense UV radiation of earth surface.

**Global Warming**: Normally the outgoing infrared radiation emitted by earth's surface is absorbed by greenhouse gases ($CO_2$, $CH_4$ and $N_2O$) and CFCs and radiate part of this energy back to earth (greenhouse flux) making the earth warm. Atmospheric greenhouse gases forming a blanket over the earth prevent escape of heat from earth's surface to outer space (greenhouse effect). Depletion of ozone layer (ozone hole) results in intense radiation of earth surface contributing to global warming.

$CO_2$ is the most abundant greenhouse gas, sources of which include fossil fuel burning, automobile exhausts, domestic fires, deforestation etc. The sources of $CH_4$ include freshwater wetlands, enteric fermentation in ruminants (cattle) and flooded rice fields and burning of biomass. CFCs are emitted out due to leaks of air-conditioners, refrigeration units and evaporation of industrial solvents. CFCs persist in environment for as long as 260 years. CFCs deplete ozone layer: 1 molecule of CFC destroys 1 lakh atoms of $O_3$.

The adverse effects of global warming include: Increase in temperature of earth's surface, shift of vegetation to low temperature areas, death of vegetation, decrease in food production, increased incidence of crop pests and diseases in man (One per cent loss of ozone : 50,000 cases of cancer or 1 lakh cases of blindness) and animals.

**Particulate Matter:**

Dusts in air (solid particles in air) cause lung disease.
Particles of 5 µm diameter or larger are deposited in upper airway (nose) and removed by sneezing.
2 – 5 µm diameter are deposited in tracheobronchial tree, cleared by upward movement of mucus by cilia.
Less than 2 µm diameter remain suspended in inspired air. Reach alveoli and are absorbed. If excess cause lung disease:
Dusts cause occupational lung diseases (Occupational Toxicology): Silicon (**Silicosis**); Asbestos (**Asbestosis**); Coal (Black Lung: **Pneumoconiosis**); Baxuite/Aluminum (Bauxite lung or **Shaver's Disease**); Cotton (Cotton lung: **Byssinosis**)

**Water Pollution**

Water pollutants are physical, chemical and biological in nature. The polluted water is unfit for human or animal use (unpotable).
**Physical Pollutants**: Mud, grit, stone, lime, ash, aquatic flora etc.
Source: Soil waste, animal wastes, street refuse, municipal wastes, industrial effluents and water run off from mines and brick kilns. Increase ambient temperature of water and Decrease soluble $O_2$.
**Chemical pollutants**: Pollute both surface and groundwater. Are both natural and manmade: Mineral salts, metallic ions: Carbonates, bicarbonates, nitrates, sulfates, chlorides of Ca, Mg and Na. Metals: Lead, iron, arsenic, cadmium, fluorine etc; petrochemical wastes, brine (salt solution from tanneries), fertilizers, pesticides etc.
**Acid rain**: Decrease in pH of surface water: Leach Ca, Mg, K and Na out of the soil into groundwater: Infertility of the soil. Excessive salts: Salinity: Decrease plant growth and affect health and productivity of livestock.
**Biological pollutants**: Aquatic fauna are the major source. Planktons: Plants and animals, sponges, worms, algae, snails etc. Dead planktons decrease DO (dissolved oxygen). Bacteria (*Salmonella typhi*, *Shigella* spp., *E. coli* etc) cause water borne diseases and jaundice.

## 7. Radiation Hazards

**Radiation Toxicology**: Branch of toxicology deals with the study of adverse effects of ionizing radiation on living organisms.

**Radiation Injury**: Injury due to exposure to ionizing radiation.

**Sources of Radiation**:

Natural:

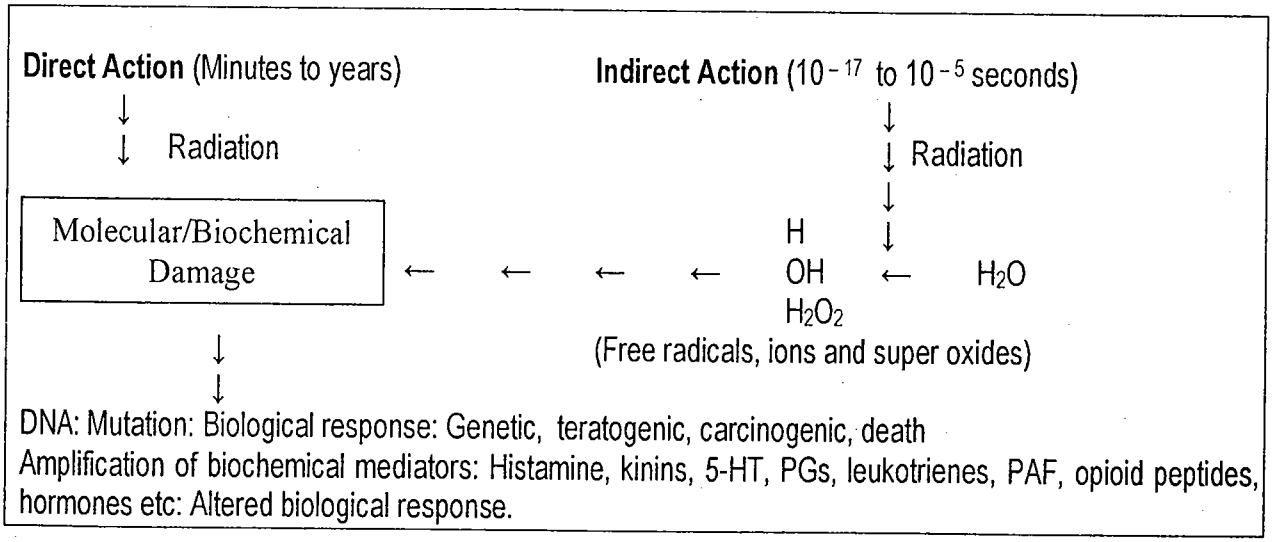
1. Geochemicals in soil and rocks: Uranium $^{238}$, Uranium $^{235}$, Thorium $^{232}$, Radon $^{222}$, Thoron $^{220}$, Thoron $^{232}$ etc.
2. Solar radiation: UV radiation (more intense due to depletion of ozone layer)
3. Cosmic radiation

Manmade:

1. Accidents in nuclear reactors
2. Fall out of nuclear explosions
3. Occupational exposure to radioactive materials (Industries, medicine, agriculture, power).
4. Therapeutic/Diagnostic exposure (over dosage/exposure: Cancer treatment/X-ray).
5. Improper disposal of radioactive wastes (Contamination of vegetation and water)

**Radiation Damage**: Results in irreversible cytotoxicity, characterized by mutagenecity; teratogenecity, carcinogenicity; specific cell or tissue death and metabolic alterations

**Mechanism of Radiation Injury**:


Direct Action (Minutes to years)
Radiation
Molecular/Biochemical Damage
Indirect Action (10 - 17 to 10 - 5 seconds)
Radiation
H
OH
H2O2
H2O
(Free radicals, ions and super oxides)
DNA: Mutation: Biological response: Genetic, teratogenic, carcinogenic, death
Amplification of biochemical mediators: Histamine, kinins, 5-HT, PGs, leukotrienes, PAF, opioid peptides, hormones etc: Altered biological response.

The indirect action of radiation results in formation of ion pairs. The ion pairs interact with themselves and other surrounding molecules to form free radicals and hydrogen peroxide, which cause molecular and biochemical damage.

Direct action of ionizing radiation leads to molecular/biochemical damage in the form of expression of damaged DNA, stimulation/suppression of release of biological mediators, causing abnormal organ function/cell death.

Radiation interacts with matter resulting in formation of ions and free radicals. Water is the most abundant molecule in living systems (55-60%). Water is first target of irradiation in the body.

**Radiolysis of water:**

Radiation

Water → $H_2O^+$ (ionized water molecule) + $e^-$ (free electron)

The free electron interacts with water to form hydrated electron

$e^- + H_2O \rightarrow H_2O^-$ (hydrated electron)

The ionized water molecule decomposes to form hydroxyl free radical

$H_2O^+ \rightarrow H^+ + OH^*$

The hydrated electron ($H_2O^-$) decomposes to form hydrogen free radical.

$H_2O^- \rightarrow OH^- + H^*$

Radiolysis water in the presence of oxygen also results in formation of superoxide and hydrated ion, which combine to form hydrogen peroxide.

Oxygen

$H_2O \rightarrow HO_2^* + HO_2^- \rightarrow H_2O_2$

The end products of radiolysis of water are $H^*$, $OH^*$, $H^+$, $OH^-$ and $H_2O_2$

The free radicals have unpaired electron in outer electron shell. The free radicals are highly reactive and attack a variety of nearby biomolecules. Hydrogen peroxide oxidizes many macromolecules.
Thus formation of free radicals and hydrogen peroxide results in a multitude of adverse biochemical changes, denaturing the normal cellular constituents:
Amino acids: Liberation of ammonia, $H_2S$, pyruvic acid, $CO_2$ and $H_2$
Carbohydrates: Breakdown
Lipids: Peroxidation
Proteins: Degradation and destruction of thiol groups (SH containing enzymes)

**Biological Effects of Radiation Injury: Rapidly dividing tissues are most affected (DNA)**

1. Bone Marrow Suppression: Most sensitive: Decrease in immune competency (No formation of T and B lymphocytes), Blockade of macrophage function/phagocytosis (decrease in monocytes and neutrophils), decrease in mature erythrocytes, thrombocytopaenia (haemorrhages) and leukaemia.
2. Reproductive system: Infertility in female (ovarian failure) and sterility in males (atrophy of testes, prostrate and seminal vesicles). Disapperance of germinal cells, azospermia and aspermia: **Dividing cells most sensitive**).
3. Digestive system: Mucosa: Necrosis and denudation: Loss of fluid and electrolytes. Bacteraemia. Impairment of acid secretion and enzyme activities.
4. Cardiovascular System: Circulatory shock (hypotension) : The cardiovascular responses are precipitated by the release of histamine, 5-HT, opioid peptides, eicosanoids and catecholamines
5. Urinary System: Nephropathy: Impairment of renal function.
6. Liver: Degeneration and jaundice
7. Lungs: Pneumonitis, Pulmonary oedema and fibrosis.
8. Endocrines: Failure of hypothalamic-pituitory system, hypothyroidism, hyperparathyroidism (increase in $Ca^{++}$ loss) and increased plasma corticosteroids: adrenal cortical atrophy.

10 Skin: Radiation dermatitis. Erythema to necrosis. Hyperkeratinization..

## 8. Chemical Warfare Agents

These are weapons of Mass Destruction. These include chemical poisons or highly virulent microbes/toxins (Anthrax). Systemic Poisons:

A. Lethal:
   i. Cyanide, HCN and cyanogen bromide
   ii. Nerve gases : Tabun, Sarin, Soman and DFP (OP AntiChEs)
   C. Lung Irritants: Respiratory distress: Chlorine and Phosgene gases.
   D. Lacrimators: Tear gas shells : Riot Control: Acrolein
   E. Sternutators: Severe discomfort: persistent sneezing and vomition; Aresenical smokes: Adamsite.
   F. Vesicants: Harassing Agents: Blisters on skin, pulmonary oedema and blindness :
   i. Mustards : Dichloroethylsulfide, Lewisite and Mustine
   ii. Nettle Gas (Arsenical gas).

## EXERCISE

1. List the common toxicants found in animal feeds along with their source and describe in brief their toxicology and treatment.
2. What is environmental pollution? Enlist the different sources of environmental pollution. Discuss the mode of biological transfer of pollutants along the food chain.
3. Classify the air pollutants and discuss their adverse effects on animals.
4. What are the sources of radiation injury? Describe the biological effects of radiation injury.
5. **Write a short note on the following**:
   a) Food chain
   b) Biomagnification
   c) Gossypol poisoning
   d) Subabul toxicity
   e) Ionophore toxicity
   f) Air pollution
   g) Water pollution
   h) Global warming
   i) Green house gases
   j) Radiation injury
   k) Radiolysis of water
   l) Mechanisms of radiation injury
   m) Biological effects of radiation injury
   n) Chemical warfare agents
   o) Chocolate poisoning in dogs
   p) Oestrogen feed additive toxicity
6. **What do you mean by the following (Define)? Answer in one or two sentences for each**:
   a) Pollution
   b) Environmental pollution
   c) Environmental toxicology
   d) Biomagnification
   e) Global warming
   f) Green house gases
   g) Acid rain
   h) Ozone layer
   i) Silofillers disease
   j) Photochemical smog
   k) PAN
   l) Silicosis
   m) Penumoconiasis
   n) Shaver's disease
   o) Byssinosis
   p) Radiation injury
   q) Free radicals
   r) Super oxide
   s) Direct radiation injury
   t) Indirect radiation injury
   u) Radiolysis of water
   v) Chemical warfare agent
   w) Nerve gases
   x) Strenutators
   y) Vesicants
   z) ppm/ppb/ppt
   aa) Residue
   bb) Withdrawal period
   cc) ADI
   dd) NOEL/NOAEL/MNAEL
   ee) EMRL/MRL/RfD
   ff) Tolerances
   gg) Finite tolerance
   hh) Negligible tolerance
   ii) Zero tolerance
   jj) Gossypol
   kk) Mimosine
   ll) Linamarin
   mm) Sinigrin
   nn) Progoitrin
   oo) Solanine
   pp) Inophores
   mm) Probiotics
   nn) UV radiation
   oo) Ionizing radiation
   pp) Ozone hole
   qq) Greenhouse flux
   rr) Greenhouse effect
   ss) LOAEL/LOEL

7. **Matching** (parallel pairs):
   a) Endotoxins: Food infection
   b) Exotoxins: Poisoning
   c) Anabolics: Growth promoters
   d) Trypsin inhibitor: Antinutrient
   e) Phytates/Lectins: Antinutrients
   f) Gossypol: Cotton seed cake
   g) Mimosine: *Leucaena leucocephala*
   h) Phytates: Til cake
   i) Sinigrin: Mustard cake
   j) Glucosinolate: Progoitrin
   k) Dimethyldisulfide: Hemolytic
   l) *Allium* spp: Dimethyldisulfide
   m) Progoitrin: Rape seed cake
   n) Thiocyanate: Goitrin
   o) Solanine: Glycoalkaloid
   p) DDT: Biomagnification
   q) Sulfur dioxide: Acid rain
   r) Methanol: Blindness
   s) Benzene: Carcinogen
   t) CO: Anoxia
   u) Ozone layer: Filters UV radiation
   v) Methane: Greenhouse gas
   w) CFCs: Deplete ozone
   x) Silicosis: Silicon dust
   y) Pneumoconiasis: Coal dust
   z) Shaver's disease: Bauxite lung
   aa) Byssynosis: Cotton lung
   bb) Mutation: Direct radiation damage
   cc) Free radicals: Indirect radiation injury
   dd) Tabun/Sarin/Toban: Nerve gas
   ee) Phosgene: Lung irritant
   ff) Lewisite: Arsenic
   gg) Acrolein: Teargas
   hh) Phenylbutazone: Doping agent
   ii) Barbiturates: Euthanasia
   jj) Subabul: Mimosine, 3,4-DHP/2,3-DHP
   kk) Mimosine: Alopecia/Goitrogenic
   ll) Chocolate: Theobromine/Adenosine antagonism
   mm) Poultry litter: Oestrogenism
   nn) Brewer's residues: Aflatoxicosis
   oo) Chocolates: Xanthine toxicity
   pp) Chocolates: CNS toxicity

8. **Differentiate between the following**:
   a) Slaughter and euthanasia
   b) Ethanol and methanol
   c) $O_2$ and $O_3$
   d) Vesicants and sternutators
   e) Sacrifice and euthanasia
   j) Direct radiation injury and indirect radiation injury
   k) Feed additive and feed contaminant
   l) Ozone in stratosphere and atmosphere
   f) ADI and NOAEL
   g) ADI and RfD
   h) Finite tolerance and zero tolerance
   i) Negligible tolerance and zero tolerance
   m) Mimosine and monensin
   n) LOEL and NOEL

9. **Mention the source/cause of the following**:
   a) DDT pollution in environment
   b) Benzene in air
   c) PAN in atmosphere
   d) Methane in air
   e) CFCs in atmosphere
   f) Biological water pollutants
   g) Chemical water pollutants
   h) Agricultural pollution
   i) Geochemical radiation
   j) Gossypol
   k) Mimosine
   l) Inophores/Monensin
   m) Linamarin
   n) Solanine

10. **Give the most appropriate reason for each of the following statements**:
   a) Clinical signs following exposure to toxins appear immediately.
   b) Clinical signs following food infection are delayed.
   c) Tannins, lectins, phytates and trypsin inhibitors are called antinutrients.
   d) Chocolate feeding can cause toxicity in dogs.
   e) Cotton seed cake is treated with calcium carbonate (1%) before feeding to livestock.
   f) Rape seed cake feeding may cause hypothyroidism.
   g) Ionophore feeding interferes with normal rumen function.
   h) Excess ionophore concentration in feed is toxic.
   i) DDT concentration increases in the upward direction of food chain.
   j) Sulfur dioxide pollution results in acid rain.
   k) Methanol causes blindness.
   l) PAN retards plant growth.
   m) Acid rains cause soil infertility.
   n) Acrolein is used for riot control.
   o) Ozone has harmful effects in atmosphere.
   p) Ozone has a protective role in stratosphere.
   q) Ethanol is the antidote of methanol intoxication.
   r) 4-methyl pyrazole is the antidote in methanol poisoning.

s) Chronic exposure to automobile emissions may cause aplastic anaemia/leukaemia.
t) Silage fillers may develop pulmonary oedema.
u) Ozone has beneficial as well as harmful effects.
v) Greenhouse gases increase the environmental temperature.
w) Global warming is attributed to greenhouse gases.
x) Stray cattle also contribute to greenhouse effect.
y) Air pollution of CFCs results in elevated temperature of earth's surface.
z) Global warming adversely affects environment/ecosystem.
aa) Health hazards of air pollution due to particulate matter are inversely related to size of the particles.
bb) Dead planktons cause water pollution/deteriorate water quality.
cc) Biological pollution of water causes water borne diseases and jaundice.
dd) The consequences of injury due to direct actions of ionizing radiation are delayed.
ee) The consequences of injury due to indirect actions of ionizing radiation are noticed immediately.
ff) The indirect actions of radiation injury result in biological/biochemical damage.
gg) The direct actions of radiation injury result in teratogenic/carcinogenic effects.
hh) The direct actions of ionizing radiation cause molecular/biochemical damage.
ii) Radiation injury is characterized by immunosuppression.
jj) Radiation injury is characterized by haemorrhages.
kk) Radiation injury in males is characterized by sterility.
ll) Radiation injury in females is characterized by infertility.
mm) Nerve gases as chemical warfare agents cause systemic toxicity.
nn) NOAEL is more that ADI
oo) DDT is assigned zero tolerance in foods or food products
pp) Excess ionophore feeding is toxic to poultry birds.
qq) Poultry litter feeding may become toxic to cattle.
rr) Residue from brewer's plants may be toxic to the animals.
ss) Formalin fortification of grains to dairy cows should be with caution.
tt) Caustic-treated grains are toxic to ruminants.
uu) Feeding poultry waste may result in testicular retardation in steers or male lambs.

# CHAPTER – 50: DOPING, EUTHANASIA AND DRUG TOXICITY

## 1. Doping

Doping is dministration of a pharmacologically active agent for improving the physical performance and/or hiding a physical defect or impairing the physical performance in man or animals. Generally adopted unscrupulously in animals to hide lameness or pain or increase athletic performance of race horses.

Dope: The agent used for doping.

Dope Test: Test to detect the parent dope molecule or its metabolite in body fluids (saliva, blood or urine).

Doper: Person who does doping.

**Drugs Commonly Used for Doping**:

Anabolic steroids: Sex hormone Testosterone, Corticosteroids, Antihistamines, Analgesics Antiinflammatory agents, Local anaesthetics, Muscle relaxants, Respiratory stimulants.

Diuretics: To cause rapid excretion of dope or decrease in body weight (water loss).

**Genetic Doping**: Induction of enhanced synthesis of hormones through introduction of specific genes.

## 2. Euthanasia

It is the process of killing an animal without causing pain. Euthanasia is humane killing of animals by a veterinarian upon request of the owner of the animal under specific circumstances:

1. To relieve from undue suffering: incurable disease or extremely painful conditions.
2. If the animal becomes unfit for the purpose of its maintenance.
3. If the animal becomes dangerously aggressive or rabid

**Ideal Euthanatizing Agent:**

1. Should cause death smoothly without causing any struggling or pain.
2. The agent is sure to cause death.
3. Should be easily administrable
4. Should be safe for the handling person
5. Should not be a cause of environmental insanitation or contamination.
6. Inexpensive.

**Euthanatizing Agents:**

1. Barbiturates: i/p, i/v or i/cardiac in small animals.
2. Chloral hydrate: i/v in large animals.
3. Saturated solution of magnesium sulfate (1:1) i/v in small or large animals.
4. Inhalation Anaesthetics: Ether or chloroform in dogs, cats, birds or rodents (pretreat with tranquilizers to prevent, howling, excitement or struggling).
5. Carbon Monoxide (Chamber): Dogs and cats (pretreat with tranquilizers to prevent excitement or struggling).

**Ideal Agent**: Pentobarbitone (6.6 G) + Chloral hydrate (30 G) + Magnesium sulfate (15 G) in 1000 ml water i/v : Rapid respiratory failure and cardiac arrest without causing muscular twitchings or spasms.

## 3. Drug Toxicity

| Sr.No. | Drug/Drug Class | Major Toxic Sign/Symptom | Antidote/Treatment |
|---|---|---|---|
| 1 | Acepromazine | CNS/Respiratory/CVS depression | CNS stimulants. Adrenaline is contra-indicated |
| 2 | Adrenaline | Cardiac arrhythmia (increased in halothane/ cyclopropane/chloroform etc anaesthesia) | Beta-adrenoceptor blockers or piperoxon |
| 3 | Antihistamines | Nervous signs: Incordination, hyperexcita-bility, tremors, convulsions & CV failure | Sedatives or US acting barbiturates (avoid excessive sedation) |
| 4 | Apomorphine | CNS stimulation | Tranquilizers |
| 5 | Aspirin | Cat: Most sensitive: Hematemesis, dyspnoea, hyperpnea and hepatitis. Dog: Restlessness, convulsions, hematemesis and peptic ulcer. Pulmonary oedema in sheep. | Gastric lavage with soda bicarb., saline purgatives, antacids, $H_2$ blockers; GI mucosal protectants. |
| 6 | Atropine | Constipation, mydriasis, tachycardia, hyperpnea, restlessness, ataxia, tremors or convulsions | Neostigmine and phenobarbiturate |
| 7 | Barbiturates | Central respiration failure | Analeptics/Artificial respiration |
| 8 | Benzodiazepines | CNS depression (CV & respiration depression) | Flumazenil/Symptomatic |
| 9 | Cephalosporins | GI disturbances, hypersensitivity/allergic reactions. Prolonged use: Neutropenia, thrombocytopaenia and renal impairment | Antihistamines, haematinics |
| 10 | Chloral hydrate | Central respiration failure and hypotension | Analeptics |
| 11 | Chloramphenicol | Bone marrow suppression | Discontinue therapy. Hematinics |
| 12 | Chlorpromazine | Ataxia and CNS depression. Not to be used in horses (abnormal gait, incoordination: stumbling/falling). | Symptomatic. Adrenaline is contraindicated |
| 13 | Cholinergics | Colic, diarrhea and hypotension | Muscarinic blockers. |
| 14 | Curariform drugs | Respiration failure (peripheral) | Neostigmine. Analeptics. |
| 15 | Digitalis | Diarrhoea, emesis, depression, cardiac arrhythmia and weight loss | Potassium infusion, atropine & symptomatic |

| | | | |
|---|---|---|---|
| 16 | Droperidol + Fentanyl Anaesthsia | Salivation, defecation, respiratory depression, bradycardia, woody-chest syndrome, rigidity of neck, tonic convulsions in dog. CNS excitation in pig, cat & ruminants. | Atropine premedication (0.045 mg/kg. 4-aminopyri-dine (0.5 mg/kg + naloxone (0.04 mg/kg) iv in dog. |
| 17 | Ivermectin | CNS depression & ataxia in horse. | Symptomatic |
| 18 | Ketamine | Tremors/convulsions | Diazepam |
| 19 | Ketamine + Xylazine | Salivation, tremors/ convulsions | Cat: 4-aminopyridine (0.6 mg/kg) + yohimbine (0.25 mg/kg iv; Horse: 4-aminopyridine (0.2 mg/kg) iv. |
| 20 | NSAIDs | Gastric ulceration, nausea, vomition & CNS excitation. Cats more sensitive. | Same as aspirin |
| 21 | Penicillins | Allergic/hypersentive reactions. In addition salivation, shivering and vomition in dog. | Antiallergic therapy. Antiemetics. |
| 22 | Phenol/Cresol | Cat: Most sensitive: Resp. failure, GI disturbances, convulsions, coma & death | Demulscents, gastric lavage, wash skin with water & soap. |
| 23 | Phenothiazine (Anthelmintic) | Photosensitization of unpigmented body surfaces (keratitis), except in horse. Horse: hemolysis, jaundice, anaemia & hemoglobinuria. | Therapy for photosensitization & liver tonics. Blood transfusion in horse. |
| 24 | Phenothiazine Tranqilizers | Respiration and CV depression. Hepatic insufficiency | Respiration & CV stimulants. Hepatotonics |
| 25 | Phenylbutazone | Colic, diarrhea, depression, gastric ulcers, renal impairment. Horse most sensitive | Gastric lavage with soda bicarb. Antacids, $H_2$ blockers & GI mucosal protectants. |
| 26 | Streptomycin and other aminoglycoside antibitotics | Restlessness, dyspnoea, vestibular, auditory & renal toxicity. Synergistic curariform effect with ether or NM blockers. | Discontinue therapy |
| 27 | Sulfonamides | Poultry: Hypothrombocytopenia, peripheral neuritis and low egg production. Cat & Dog: Hpersentive/ allergic reactions and crystalluria | Hematinics in birds. Rehydration with urinary alkalizers. Antiallergy therapy. |
| 28 | Xylazine | CNS excitation, convulsions & hypotension in horse. Bradycardia, hypotension & bloat in dog. CNS depression in cattle. Abortion. | Symptomatic. Adrenaline contraindicated. |

**EXERCISE**

1. Write a short note on a) Doping b) Euthanasia

2. **What do you mean by the following**? Answer in one or two sentences for each:
   a. Euthanasia
   b. Doping
   c. Doper
   d. Dope test
   e. Doper
   f. Ideal Euthanatizing agent

3. **Matching** (Parallel Pairs):
   a. Phenylbutazone: Dope
   b. Barbitrates: Euthanasia
   c. Adrenaline: Cardiac arrhythmia
   d. Aspirin/NSAIDs: Peptic ulcer
   e. Chloramphenicol: Bone marrow depression
   f. Phenol/Cresol: Toxic to cat/dog
   g. Ivermectin: Ataxia in horse
   h. Barbiturates: Respiration failure
   i. Streptomycin: Vestibular/Renal/Ototoxicity
   j. Sulfonamides: Crystalluria

4. **Give the most appropriate reason for each of the following statements:**
   a. Use of phenylbutazone is unlawful in race horses.
   b. Strychnine is banned as an ethanatizing agent to kill stray dogs.
   c. Tranquilizers are adjuncts in euthanasia of dogs/cats.
   d. A solution of pentobarbitone, chloral hydrate and magnesium sulfate is an ideal euthnatizing agent